Comparison of the Short term Efficacy and Serum Markers between Lobaplatin/Paclitaxel and Carboplatin/ Paclitaxel-based Adjuvant Chemotherapy in Patients with Ovarian Cancer

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The present study was aimed to compare short-term therapeutic efficacies and related changes of serum markers from 2 chemotherapeutic regimes using lobaplatin or carboplatin in combination with paclitaxel in ovarian cancer patients after cytoreductive surgery. Sixty patients were recruited with confirmed ovarian cancer. Patients were equally and randomly divided into 2 groups receiving paclitaxel with lobaplatin or carboplatin, respectively. Follow-up was made 6 months post-treatment. The therapeutic efficacy, serum levels of cancer antigen 125/mucin 16 and human epididymis protein 4 as well as the quality-of-life were assessed before and after treatment. No significant difference in therapeutic efficacy was observed between the groups. The response rates at 1, 3 and 6 months were 76.7 % (23/30), 66.7 % (20/30) and 46.7 % (14/30) in the lobaplatin group and 73.3 % (22/30), 63.3 % (19/30), 36.7 % (11/30) in the carboplatin group, respectively. At the end of the chemotherapy, serum levels of human epididymis protein 4 and cancer antigen 125 in both groups returned to normal. However, patients in the lobaplatin group had significantly higher human epididymis protein 4 and cancer antigen 125 levels than those in the carboplatin group when examined at 3 or 6 month after chemotherapy ($p<0.05$). Moreover, at the end of follow-up, the quality-of-life score-C30 of the lobaplatin group was better than that of the carboplatin group with statistical significance ($p<0.05$). Both lobaplatin and carboplatin exert sufficient antitumor efficacy to be included in the standard platinum/ paclitaxel-based chemotherapy against ovarian cancer. Lobaplatin, on the other hand, has demonstrated higher efficacy to control the progress of the disease yet less toxicity to warrant better patient quality-of-life.

Key words: Ovarian cancer, lobaplatin, carboplatin, paclitaxel, CA125, HE4

Ovarian cancer is one of the most lethal gynecologic malignancies, the patients with 5-year survival rate is approximately 30 %[1-3]. Due to the absent or indistinctive early-symptoms, about 70 % ovarian cancer patients are diagnosed only at advanced stage with metastases beyond the pelvic cavity and substantially poor prognosis[4]. Several serological markers have been widely used in clinical practice to monitor the progression and predict the prognosis of ovarian cancer, among which cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) are the most common ones[5-8]. Both CA125 and HE4 are secretory proteins specifically expressed in ovarian tumor tissues at high levels to warrant decent sensitivity and reliability for advanced stage cancers[9,10].

Standard clinical management of ovarian cancer includes upfront cytoreductive surgery followed by platinum/taxane based chemotherapy[1,2]. Paclitaxel (PTX) plus carboplatin (CBP) is the most widely used combination with good clinical response and tumor remission upon the completion of treatment cycles[11]. Nevertheless, CBP is frequently not well tolerated in a significant portion of Chinese patients. Severe side effects of CBP include fatigue, renal failure, bone marrow suppression, gastrointestinal dissatisfaction, and deteriorated quality-of-life (QOL), which ultimately results in limited dosage, delaying or even termination of the chemotherapy[12-14]. It is therefore critical to identify novel platinum analogues that are less toxic yet with comparable or superior antitumor efficacy than CBP. One of such compounds is lobaplatin (LBP, cis-(trans-1,2-cyclobutanebis (metylamine)-S-lactate-O^1,O^1)platinum), which has been tested as a single agent by several Phase I/II clinical trials

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and has demonstrated strong tumor suppressive activity with significantly milder side effects[15-17]. In addition, robust tumor suppressive activity of LBP against ovarian cancer has been demonstrated *in vitro* by cell culture systems[18]. Recently, LBP has been approved by China Food and Drug Administration in the treatment of advanced breast cancer, small cell lung cancer and chronic myelogenous leukemia[19,20]. Nevertheless, clinical studies remained scanty to investigate the efficiency and compatibility of LBP to be involved into the first-line platinum/taxane based chemotherapy for ovarian cancer patients. In this study, the clinical efficacy and serological changes of 60 post-surgical ovarian cancer patients randomly assigned to chemotherapies consisting of PTX in combination of either LBP or CBP was compared.

MATERIALS AND METHODS

Patient cohort and treatment:

Sixty ovarian cancer patients hospitalized between October 2013 and August 2015 have been chosen as subjects for this study. Prior to the commencement, the study proposal has been reviewed and approved by the Ethnic Committee of Affiliated Hospital of Beihua University with signed informed consent obtained from each patient willing to participate. All procedures performed in studies involving human participants were in accordance with the ethical standards of Affiliated Hospital of Beihua University research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The age of patients ranged from 58 to 75 y with a median age of 65.7 y. The tumour tissue specimens obtained from cytoreductive surgery had been pathologically verified to be primary ovarian cancer. All patients presented tumour beyond ovaries, including 6 at International Federation of Obstetrics and Gynecology (FIGO) stage II, 47 at FIGO stage III and 7 at FIGO stage IV. Thirty-four patients had serous adenocarcinoma and 26 patients had mucinous adenocarcinoma.

To be eligible for this study, patients had to fulfil the following criteria, first diagnosed with primary ovarian cancer; no prior treatment other than the primary cytoreductive surgery; optimal outcome of cytoreductive surgery with the maximum diameter of residual disease less than 1 cm; serum CA125 level> 35 U/ml and HE4>150 pmol/l; and adequate hepatic and renal functions and normal blood and electrocardiogram test. Patient presenting one of the following signs were deemed ineligible and immediately removed from the study, those receiving any neoadjuvant chemo- or radio-therapies prior to the cytoreductive surgery; severe post-surgical functional impairment (Karnofsky performance scale <70); contraindicative, allergic or intolerance to any of the chemotherapeutic agent administrated and an estimated life expectancy of less than 6 mo.

The 60 recruited ovarian cancer patients were equally (30 each) randomized into treatment groups receiving PTX+LBP or PTX+CBP. The distribution of patient age, FIGO stage and histo types between the groups were equal (Table 1). Standard dosages of CBP and PTX were employed according to the recent United States Gynecologic Oncology group phase III clinical trial (GOG-0182)[11]. The dosage of LBP was chosen based on a previous phase II and pharmacokinetic study[15]. Chemotherapy was administrated 1 w after primary cytoreductive surgery. In the PTX+LBP group, for each treatment cycle, patients were intravenously administrated (iv) with 135-175 mg/m^2 on d 1 followed by iv of LBP at a dose of 50 mg/m^2 on d 2. Same PTX and LBP treatment was repeated after 21 d to complete the treatment cycle. Totally, 3 cycles were administrated with a 3-4-w interval between each cycle. Similar treatment cycles were applied to the PTX+CBP group, with the LBP replaced by a 3-d constitutive CBP treatment at 50 mg/m^2/d on d 1, 2 and 3. In addition, the following pre-treatment was applied to all patients. One day prior to chemotherapy, patients in both groups were intravenously hydrated with 2500-3000 ml saline. Two doses of dexamethasone (20 mg) were given at the night before chemotherapy (PTX or platinum compound) orally and in the same morning

TABLE 1: CHARACTERISTICS OF PATIENTS TREATED WITH PTX IN COMBINATION LBP OR CBP

Character	PTX+LBP Group, n=30	PTX+CBP Group, n=30	P
Age (year), mean±sd	65.3±3.6	65.9±2.9	0.48
Histological subtype, n (%)			0.602
Serous	16 (53.3)	18 (60.0)	
Mucinous	14 (46.7)	12 (40.0)	
FIGO stage, n (%)			1
II a	3 (10.0)	3 (10.0)	
II b	23 (76.7)	22 (73.3)	
III a	4 (13.3)	5 (16.7)	

PTX- paclitaxel, LBP- lobaplatin, CBP- carboplatin

of the chemotherapy. Immediately (30 min) prior to chemotherapy, another 5-10 mg of dexamethasone was given intravenously. All patients were closely monitored for hepatic and renal function as well as hemogram. Dosage reduction (10 mg/m^2.d) of CBP or LBP would be applied for those eliciting bone marrow suppression. All patients had completed the scheduled treatment. This study was approved by the Ethics Committee of Affiliated Hospital of Beihua University.

Serological tests and treatment assessment:

Serum specimens were collected from fasting patients. Serum levels of CA125 and HE4 was examined using chemo luminescent method and ELISA respectively, following the manufacturer's instructions. The detection kit was obtained from Depp Corporation of America.

Evaluation of therapeutic efficacy and toxicity:

Treatment efficacy was evaluated using the WHO Response Evaluation Criteria In Solid Tumors (RECIST) criteria[21]. Complete response (CR) was defined as disappearance of disease for at least 4 w. Partial response (PR) was used to describe reduction of the lesion volume by at least 50 % for at least 4 w. The response rate (RR) was calculated by the sum of CR and PR. Chemotherapy related acute or sub-acute toxicities were evaluated based on the WHO Toxicity Grading Scale for Determining the Severity of Adverse Events as well as the National Cancer Institute Common Toxicity Criteria (CTCAE 4.0). A grading system of Grade 0-IV was employed to describe the degree of toxicity.

Statistical analysis:

SPSS 19.0 was used for statistical analyses. Measurements were presented as mean±standard deviation. Comparison of the means of two groups was done by pairwise or independent Student's t-test when the statistics approximated to normal distribution. Otherwise, non-parametric Wilcoxon test was used instead. A repeated measure ANOVA was used for analysing the CA125 and HE4 tumour markers. Chi-square test or Fisher exact test was used to compare categorical data presented as percentage. All statistical tests were two-tailed and a p-value less than 0.05 were deemed as statistically significant.

RESULTS AND DISCUSSION

Short-term clinical response was evaluated monthly after the completion of chemotherapy. No significance in RR was observed between the LBP and CBP groups, so as the overall survival rate at 6 mo (Table 2). No statistically significant difference of pre-treatment HE4 or CA125 levels was observed in patients assigned to LBP group or CBP group. In contrast, significant lower HE4 and CA125 level was observed in patient receiving PTX+LBP regime, suggesting LBP might have higher therapeutic efficacy than CBP (Table 3).

Adverse effects upon chemotherapy were primarily elicited as hepatic toxicity (elevation of aspartate aminotransferase or alanine transaminase, bone marrow suppression and gastrointestinal reactions. Most side effects were restricted between Grade 0 to II and could be effectively alleviated upon active symptomatic treatment. No patient in either group was

TABLE 2: SUMMARY OF CLINICAL RESPONSE BETWEEN THE LBP AND CBP GROUPS

Outcome	PTX+LBP group, n=30	PTX+CBP group, n=30	P
Response rate (RR), n (%)			
1 month	23 (76.7)	22 (73.3)	0.766
2 months	20 (66.7)	19 (63.3)	0.787
3 months	14 (46.7)	11 (36.7)	0.432
Survival at 6 months, n (%)	24 (80.0)	21 (70.0)	0.371

TABLE 3: COMPARISON OF OVARIAN CANCER SEROLOGICAL MARKERS BEFORE AND AFTER CHEMOTHERAPY

Group	Pre-treatment		1-month post-treatment		3-month post-treatment		6-month post-treatment	
	HE4	CA125	HE4	CA125	HE4	CA125	HE4	CA125
PTX+	687.5±	997.4±1	122.3±	25.7±	148.9±	102.6±	368.3±	547.2±
LBP	44.8	26.4	22.6	9.3	27.4	41.4	43.7	68.8
PTX+	696.7±	1032.6±	128.7±	27.4±	169.7±	134.4±	497.5±	783.7±
CBP	49.7	118.7	27.4	14.8	32.5	65.3	52.6	76.9
P	0.4544	0.2708	0.3278	0.5963	0.0096	0.0281	<0.001	<0.001

Comparison of serological biomarkers such as cancer antigen 125 (CA125) and human epididymis protein 4 (HE4) before and after chemotherapy. HE4 and CA125 were measured as pmol/l and u/ml, respectively

removed without completion of treatment cycles due to intolerance. Patients in the LBP group had significant lower incidence of bone marrow suppression ($\chi 2$=5.4060, p=0.0201). No statistical significance was observed for the incidence of other types of chemotherapy related side effects (Table 4).

At the end of 6 mo after the completion of chemotherapy, 6 (20.0 %) and 9 (30.0 %) patients deceased in the LBP and CBP groups, respectively. No statistical difference in mortality rate was suggested ($\chi 2$=0.3556, p=0.5510). The patients were further assessed about their QOL using a QOL questionnaire C30 (QLQ-C30) developed by the European Organization for Research and Treatment of Cancer (EORTC). Except for fatigue, difficult breathing and financial hardship, patients assigned in the LBP group outperformed those in CBP group for all other testing items with statistically significant differences (Table 5).

Upfront cytoreductive surgery remains the primary clinical approach for the management of patients with primary ovarian cancer[1,4]. However, even after successfully removal of all visible lesions, without the following adjuvant chemotherapy, more than 70 % patients will relapse within 6 mo after surgery. The introduction of platinum/taxane-based adjuvant chemotherapy significantly improved the overall patient outcome by increasing the post-therapy 6-mo disease-free survival rate to 60 %. It has been demonstrated through various clinical trials initiated by the US GOG that platinum/taxane regime is associated with the best RR against ovarian cancer in comparison to either doxorubicin or 5-fluorouracil[13,11]. In addition, such combinations also largely avoid single drug associated chemo resistance and has been associated with improved QOL of the patients[22,23].

Nevertheless, platinum compounds especially the first-generation reagents such as cisplatin (DDP) are often associated with severe adverse effects that sometimes leads to limited dosage and even termination of chemotherapy[14]. Recently, CBP has been demonstrate to have equivalent activity to DDP while significantly reduced nephrotoxicity, gastrointestinal toxicity and neurotoxicity, which makes CBP becomes the first-line platinum analogue in the management of primary ovarian cancer worldwide. However, CBP has been found to have intolerable side effects, especially myelotoxicity

TABLE 4: COMPARISON OF THERAPEUTIC TOXICITIES

Side effect	PTX+LBP group, n=30				PTX+CBP group, n=30				p*
	I	II	III	Sum, n (%)	I	II	III	Sum, n (%)	
Hepatic toxicity	3	1	0	4 (13.3)	4	2	2	8 (26.7)	0.197
Bone marrow	6	3	1	10 (33.3)	9	5	5	19 (63.3)	0.02
Hair loss	8	5	2	15 (50.0)	10	5	3	18 (60.0)	0.436
Gastrointestinal	8	6	0	14 (46.7)	14	3	2	19 (63.3)	0.195
Fever	13	5	2	20 (66.7)	14	7	5	26 (86.7)	0.067

PTX+LBP group- placlitaxel+lobaplatin group, PTX+CBP group- placlitaxel+carboplatin group, p-value was calculated based on comparing total incidences of the two groups

TABLE 5: PATIENT FOLLOW-UP WITH QLQ-C30 SCORING

QLQ-C30 score functional assessment	PTX+LBP group, n=30	PTX+CBP group, n=30	P
Physical function	61.7±6.5	54.5±7.8	0.002
Everyday life	58.3±4.7	51.5±5.9	0.001
Emotional function	56.3±5.3	48.1±6.4	<0.001
Cognitive function	71.4±8.7	64.7±8.3	0.012
Social Functions	57.4±10.4	50.2±9.7	0.021
Symptoms			
Fatigue	62.4±7.5	63.6±8.9	0.626
Nausea and vomiting	21.6±7.2	32.8±11.6	<0.001
Pain	37.5±10.9	49.7±10.4	<0.001
Difficulty breathing	41.4±5.4	42.9±7.2	0.43
Insomnia	43.6±7.1	49.8±9.4	0.016
Loss of appetite	48.9±6.7	56.7±7.6	0.001
Constipation	8.3±3.6	12.2±5.4	0.006
Diarrhea	30.7±6.8	37.8±7.4	0.002
Overall health assessment	47.5±9.6	41.2±10.3	0.04

(bone marrow suppression), in a substantial portion of patients in China. It thus becomes critical to identify novel platinum analogues with sufficient activity yet less toxic for those who are intolerable to CBP. LBP, a third-generation platinum analogue, becomes a promising candidate considering its strong antitumor activity, mild adverse reactions and favourable patient tolerance in a variety types of solid tumors[24]. However, systemically evaluation of the therapeutic efficacy of LBP remains scanty in ovarian cancer. A recent investigation using various ovarian cancer cell lines has suggested LBP demonstrates similar cytotoxicity as DDP or CBP in platinum sensitive cell lines *in vitro* or in xenograft based *in vivo* studies. Conversely, in platinum resistant ovarian cancer cell lines or derivative xenografts, LBP significantly outperformed DDP or CBP either as a single agent or in combination with taxanes without introducing significant side effects in host animals of the xenografts[18]. Similarly, in a phase II clinical trial, LBP has been demonstrated to have robust antitumor activity as a second-line reagent against relapsed ovarian cancer[15]. These promising pre-clinical and clinical observations warrant the test of LBP as a potential alternative first-line reagent to the routinely applied CBP which is not well-tolerated by a substantial portion of ovarian cancer patients in China.

In this study, the therapeutic efficacy and toxicity between LBP and CBP as first-line reagents in optimally cytoreduced primary ovarian cancer patients subsequently subjected to platinum/PTX-based chemotherapy were compared. Our data indicate a slightly better treatment RR in patients receiving LBP than those receiving CBP. However, no statistical significance was observed, implicating that both LBP and CBP can warrant decent therapeutic efficacy as front-line reagent after the primary surgical intervention.

Recently, serological markers such as CA125 and HE4 have become a standard in the clinical practice to monitor the tumour progression and predict the prognosis of ovarian cancer patients[9,10]. Both markers have suggested decent sensitivity and specificity to reflect the post-treatment tumour burden regardless of the type of intervention, therefore being widely used to assess the therapeutic efficacy. While there was no significant difference in the levels of CA125 and HE4 immediately (1 mo) after chemotherapy, a more drastic recurring of both serological markers was observed in patients assigned to the CBP group in comparison to those in the LBP group. This potentially implicated LBP might outperform CBP in retarding tumour relapse after tumour remission.

The main adverse effects of LBP and CBP in this study included gastrointestinal reactions, bone marrow suppression, hepatotoxicity and hair loss. Consistently with the previous reports[15,17], we do not observe any evident renal dysfunction upon LBP administration. Most adverse drug reactions were limited within CTCAE Grade 0 to Grade II, and could be effectively ameliorated upon active symptom controlling palliative care. This resulted in no patient to be taken off the treatment due to intolerable toxicity. In general, no evident difference in the incidence of adverse effect was found between the LBP and CBP groups. The only exception was bone marrow suppression, for which 5 patients in the CBP groups suffered Grade III toxicity while only 1 patient receiving LBP/PTX treatment developed Grade III toxicity. It is worth to note that the LBP related myelotoxicity is well manageable through the administration of granulocyte colony stimulating factor and thrombopoietin. This is critical for the LBP-based therapy, since thrombocytopenia is considered the major dose-limiting adverse effect in the absence of appropriate antiemetics[25].

One of the important goals of post-surgical chemotherapy is to improve patients' QOL, which can be quantitatively assessed by the QLQ-C30 scale[26-28]. The QLQ-30 scale consists of 30 items to comprehensively evaluate the subject's daily life activities through the performances in physical, psychological, social, and cognitive functions in combination with the degree of major distressing symptoms including fatigue, pain, sleep disorders, constipation and change of appetite[29]. The present data indicated that patients subjected to the LBP/PTX regime were evidently associated with better functional assessment while experienced significantly less distressing symptoms except fatigue, difficult breathing and financial hardship for which no significant difference was observed between the 2 groups. Such observation was consistent with the trend of CA125 and HE4 serological markers, implicating the decline of quality-on-life upon the more aggravated tumour progression in patients subjected to the CBP/PTX regime.

In conclusion, when combined with PTX for post-surgical adjuvant therapy against primary ovarian cancer, LBP demonstrated comparable antitumor activity as CBP. Moreover, the LBP/PTX regime may

outperform the traditional CBP/PTX regime in the short-term control of post-chemotherapy relapse and provide a better improvement of QOL. Future studies with larger patient cohorts are thus warranted to further investigate the benefit of LBP to ovarian cancer patients with different ages or clinical stages.

Conflict of interest:

No conflict of interest between any of the authors.

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