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# Combination therapy of liposomal paclitaxel and cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer

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**Summary**

*Objectives:* To investigate the efficacy and toxicities of combination therapy of liposomal paclitaxel and cisplatin as neoadjuvant chemotherapy (NACT) in locally advanced cervical cancer. *Materials and Methods:* The authors retrospectively reviewed the clinical records of patients with cervical cancer who received NACT with liposomal paclitaxel and cisplatin at Sun Yat-sen University Cancer Center from April 1, 2008 to December 31, 2012. Liposomal paclitaxel and cisplatin was administrated intravenously at a dose of 175 mg/m$^2$ and 75 mg/m$^2$, respectively. *Results:* The total response rate was 86.1% (62/72) including a complete response and partial response rate of 27.8 % (20/72) and 58.3% (42/72), respectively. Stable disease was observed in 12.5 % (9/72) of patients and progressive disease in 1.4 % (1/72). Hematological toxicities were the major dose-limiting toxicities. Grade 3/4 neutropenia and anemia developed in 18.1% (13/72) and 6.9% (5/72) of patients, respectively. Peripheral neuropathy occurred in 6.9% (5/72) of patients (all grade 1). *Conclusion:* the study findings support further evaluation of liposomal paclitaxel with cisplatin as an additional chemotherapy regimen which may be efficacious and tolerable in the NACT of cervical cancer.

*Key words:* Cervical cancer; Neoadjuvant chemotherapy; Liposomal paclitaxel; Locally advanced.

## Introduction

Cervical cancer is still the second most common malignancy in women in most low- and middle-income countries [1]. Despite the application of screening method for early disease, numerous patients present with locally advanced diseases (Stages Ib2-IVa) [2] especially in developing countries. Prognosis of this group still needs to be improved.

Treatment modality for locally advanced cervical cancer remains controversial. Concurrent radiation therapy and chemotherapy is commonly recommended [3]. However, some patients could still recur after the treatment. Furthermore, in developing areas, radiation facility may not be available. Another treatment choice is preoperative neoadjuvant chemotherapy (NACT) for two to three courses followed by radical hysterectomy [4]. Several cisplatin-based chemotherapy regimens, including combination of paclitaxel and cisplatin, have been shown to be effective against cervical cancer as NACT [4, 5].

Paclitaxel is hydrophobic and possesses a very low solubility in conventional aqueous vehicles. The preparation approved for clinical use solubilizes paclitaxel in mixture of polyethoxylated castor oil and ethanol. This vehicle may cause severe hypersensitivity reactions in humans and peripheral neuropathies [6-8].

Liposomes are a drug delivery system with diameter from 250A° to more than 20 μm and offer a flexible platform to encapsulate both lipophilic and hydrophilic drugs. It has been used to enhance the therapeutic efficacy and reduce the toxicity of several anticancer agents, including doxorubicin. Liposomal paclitaxel is a liposome-encapsulated formulation of paclitaxel. Paclitaxel liposome was found to be a viable alternative of paclitaxel because of its improved toxicological and pharmacological characteristics [9,10]. Pharmacokinetic studies in animals [10-12] have shown that liposomal paclitaxel has a longer elimination half-life and a larger volume of distribution, as compared with paclitaxel [10-12]. The concentration of liposomal paclitaxel in tissues is dramatically higher than that of paclitaxel, especially in the reticuloendothelial system, such as lymph nodes, liver, and spleen. Recent clinical trials have shown that liposomal paclitaxel and paclitaxel has similar efficacy in breast, gastric, and non-small cell lung cancer and liposomal paclitaxel has less adverse effects than paclitaxel [13-15]. In this study, the authors aim to investigate the efficacy and toxicities of combination therapy of liposomal paclitaxel and cisplatin as NACT before surgery in patients with locally advanced cervical cancer by retrospectively reviewing their data.

## Materials and Methods

The authors performed a retrospective review of the clinical records of all patients with cervical cancer who received combined therapy with liposomal paclitaxel and cisplatin at Sun Yat-sen University Cancer Center from April 1, 2008 to December 31,

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2012. The patient list was obtained from the database of Sun Yat-sen University Cancer Center. Patient hospital records were reviewed to obtain demographic data including age, diagnosis, weight, height, tumor size, stage, histology, abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), results of routine blood test, and treatment data including total cycles, doses of liposomal paclitaxel and cisplatin, date of chemotherapy delivery, and toxicities of chemotherapy. Approval was granted from the institutional review broad prior to the review of all the clinical records.

*Inclusion Criteria*

Patients who met the following criteria were included in the study: (1) a pathologically confirmed diagnosis of cervical cancer; (2) Stage I B2 - II B disease except for Stage IIA1 tumor; (3) two or three courses of combined therapy with liposomal paclitaxel and cisplatin; (4) absence of prior anti-cancer therapy.

*Treatment*

Liposomal paclitaxel was administrated by intravenous infusion over three hours at a dose of 175 mg/m$^2$ on day 1. Cisplatin was administrated intravenously at a total dose of 75 mg/m$^2$ which was infused over six hours on day 1 or was divided into two or three doses and given over three hours on day 1 to 2 or 3. The treatment was repeated every three weeks. Usually after each cycle, blood count was performed twice weekly. Granulocyte colony-stimulating factor (G-CSF) was administrated if grade 3 or 4 neutropenia developed. All patients received radical hysterectomy three to four weeks after the last course of NACT.

*Evaluation of Treatment Response and Adverse Effects*

Treatment evaluation was made based on a modification of the Response Evaluation Criteria in Solid Tumors (RECIST) [16]. Complete response (CR) was defined as the disappearance of measurable disease. Partial response (PR) was defined as a reduction of ≥ 50% in the sum of the products of the maximum and perpendicular diameters of measurable lesion. Progressive disease (PD) was defined as ≥ 25% increase in the sum of the products of maximum and perpendicular diameters of measurable lesion, or the appearance of new lesions. Stable disease (SD) was a steady state of response less than a PR or progression. Adverse effects were graded according to the National Cancer Institute (NCI) toxicity criteria [17].

To investigate the impact of different cisplatin administration method on renal function, creatinine clearance (CrCl) before chemotherapy and after two cycle of chemotherapy was calculated by the Cockcroft-Gault equation [18,19], which is as follows: CrCl (ml/min) = (140 – age (years)) × weight (kg) × 0.85 / serum Cr (mg/dl) × 72.

Statistical analysis was performed using the SPSS 16.0. Chi-square test was used to compare the difference of CrCl decrease. A $p$ value of < 0.05 was considered statistically significant.

## Results

*Patient characteristics*

A total of 72 consecutive patients were identified. The median age was 48 years (range 29-64). The number of patients with Stage Ib2, IIa2, and IIb disease was 33, 21, and 18, respectively. Sixty-three patients had squamous cell carcinoma, eight adenocarcinoma, and one adenosquamous cell carcinoma. The median tumor size at diagnosis was five cm (range 3-7) and it was greater than six cm in 12 patients. Fifty-six patients received two cycles and 16 patients three cycles of liposomal paclitaxel and cisplatin combination therapy as NACT. The total dose of cisplatin was administrated on day 1, or given dividedly on day 1 - 2, or day 1 - 3 in 13, 34, and 25 patients, respectively (Table 1).

Table 1. — *Patient characteristics (total n = 72).*

| Variables | Years/No | % |
|---|---|---|
| Age (years) | | |
| Median | 48 | |
| Range | 29~64 | |
| Stage | | |
| Ib2 | 33 | 45.8 |
| IIa2 | 21 | 29.2 |
| IIb | 18 | 25.0 |
| Histology | | |
| Squamous | 63 | 87.5 |
| Adenocarcinoma | 8 | 11.1 |
| Adenosquamous | 1 | 1.4 |
| Number of cycles | | |
| 2 | 56 | 77.8 |
| 3 | 16 | 22.2 |
| PDD administration schedule | | |
| Total dose on day 1 | 13 | 18.1 |
| Total dose dividedly on day 1 - 2 | 34 | 47.2 |
| Total dose dividedly on day 1 - 3 | 25 | 34.7 |
| Tumor size (cm) | | |
| Median | 5 | |
| Range | 3~7 | |
| < 6 | 60 | 83.3 |
| ≥ 6 | 12 | 16.7 |

*Treatment response*

All patients were assessable for treatment response. The total response rate was 86.1% (62/72) including a CR and PR rate of 27.8 % (20/72) and 58.3% (42/72), respectively. Pathologically confirmed CR was noted in 9.7% (7/72) of patients, and pathologically near complete remission (a few tumor cells were still seen after NACT), stable disease, and progressive disease in 13.9% (10/72), 12.5 % (9/72), and 1.4 % (1/72) of patients, respectively. The response rate was 84.8%, 85.7%, and 88.9% in patients with Stage Ib2, IIa2, and IIb disease, respectively. In 63 patients with squamous cell type, eight patients with adenocarcinoma, and one patient with adenosquamous cell type, the response rate was 85.7% and 87.5%, 100%, respectively. In 12 patients with tumor size equal to or greater than six cm and 60 patients with tumor size less than six cm, the response rate was 91.7% and 85.0%, respectively. The response rate was 84.6% (11/13), 88.2% (30/34), and 84.0% (21/25), in patients receiving total dose of cisplatin on day 1, or divided doses on day 1 – 2, or divided doses on day 1 – 3, respectively (Table 2).

Table 2. — *Treatment response (total n = 72).*

| Factors | CR+ PR (%) | CR (%) | PR (%) | SD (%) | PD (%) |
|---|---|---|---|---|---|
| | 62(86.1) | 20 (27.8) | 42 (58.3) | 9 (12.5) | 1 (1.4) |
| Stage | | | | | |
| Ib2 (n = 33) | 28 (84.8) | 12 (36.4) | 16 (48.5) | 4 (12.1) | 1 (3.0) |
| IIa2 (n = 21) | 18 (85.7) | 4 (19.0) | 14 (66.7) | 3 (14.3) | 0 |
| IIb (n = 18) | 16 (88.9) | 4 (22.2) | 12 (66.7) | 2 (11.1) | 0 |
| Histology | | | | | |
| Squamous (n = 63) | 54 (85.7) | 18 (28.6) | 36 (57.1) | 8 (12.7) | 1 (1.6) |
| Adenocarcinoma (n = 8) | 7 (87.5) | 2 (25) | 5 (62.5) | 1 (12.5) | 0 |
| Adenosquamous (n = 1) | 1(100) | 0 | 1 (100) | 0 | 0 |
| Tumor size (cm) | | | | | |
| ≥6 (n = 12) | 11 (91.7) | 2 (16.7) | 9 (75.0) | 1 (8.3) | 0 |
| < 6 (n = 60) | 51 (85.0) | 16 (26.7) | 35 (58.3) | 8 (13.3) | 1 (1.7) |
| PDD administration schedule | | | | | |
| Total dose on d 1 (n = 13) | 11 (84.6) | 5 (38.5) | 6 (46.2) | 2 (15.4) | 0 |
| Total dose dividedly on d 1-2 (n = 34) | 30 (88.2) | 6 (17.6) | 24 (70.6) | 4 (11.8) | 0 |
| Total dose dividedly on d 1-3 (n = 25) | 21 (84.0) | 9 (36.0) | 12 (48.0) | 3 (12.0) | 1 (4.0) |

CR: complete response; PR: partial response;
SD: stable disease; PD: progressive disease; PDD: cisplatin; d: day.

Table 3. — *Adverse effects (total n = 72).*

| Toxicity | Total (%) | G1 | | G2 | | G3 | | G4 | |
|---|---|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % | N | % |
| Gastrointestinal | | | | | | | | | |
| Vomiting | 58.3 | 11 | 15.3 | 18 | 25.0 | 10 | 13.9 | 3 | 4.2 |
| Diarrhea | 4.2 | 3 | 4.2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hematological | | | | | | | | | |
| Anemia | 59.7 | 21 | 29.1 | 17 | 23.6 | 5 | 6.9 | 0 | -0 |
| Neutropenia | 56.9 | 8 | 11.1 | 20 | 27.7 | 13 | 18.1 | 0 | 0 |
| Thrombocytopenia | 8.3 | 4 | 5.5 | 2 | 2.8 | 0 | 0 | 0 | 0 |
| Others | | | | | | | | | |
| Alopecia | 65.3 | 30 | 41.7 | 17 | 23.6 | - | - | - | - |
| Peripheral neuropathy | 6.9 | 5 | 6.9 | 0 | 0 | 0 | 0 | 0 | 0 |
| Allergy reaction | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liver impairment | 4.2 | 3 | 4.2 | 0 | 0 | 0 | 0 | 0 | 0 |

G: grade.

*Adverse effects*

All patients were assessable for adverse effects. Hematological toxicities were the major dose-limiting toxicities. Grade 3/4 neutropenia developed in 18.1% (13/72) patients. Grade 3/4 anemia occurred in 6.9% (5/72) patients. Packed red blood cells were transfused in one patient. Grade 1/2 thrombocytopenia was observed in 8.3% (6/72) patients. No grade 3/4 thrombocytopenia occurred. Nausea/vomiting was frequent with a total incidence of 58.3% (42/72), but was not dose-limiting. Peripheral neuropathy developed in 6.9% (5/72) patients (all grade 1). Other toxicities included alopecia, liver and renal impairment. Alopecia happened in 65.3% (47/72) patients, with grade 1 and 2 in 41.7% (30/72) and 23.6% (17/72) patients, respectively. Grade 3 liver impairment occurred in 4.1% (3/72). No hypersensitivity reaction was noted (Table 3). There was no treatment related death.

Table 4. — *The impact of different methods of cisplatin administration on renal function.*

| PDD administration schedule | N | CrCl decrease ≥ 10 ml/min after two cycles | | CrCl decrease ≥ 20 ml/min after two cycles | |
|---|---|---|---|---|---|
| | | N | % | N | % |
| PDD on day 1 | 13 | 7 | 53.8 | 4 | 30.7 |
| PDD on day 1-2 or 1-3 | 59 | 22 | 37.3 | 11 | 18.6 |

PDD: cisplatin; CrCl: creatinine clearance.

CrCl decrease of greater than or equal to ten ml/min after two cycles of chemotherapy occurred in 53.8% (7/13) and 37.3% (22/59) patients, respectively, in group receiving cisplatin on day 1 and in group receiving cisplatin on day 1-2 or 1-3. The difference was not significant ($p > 0.05$).

CrCl decrease of greater than or equal to 20 ml/min after two cycles of chemotherapy occurred in 30.7% (4/13) and 18.6% (11/59) patients, respectively, in group receiving cisplatin on day 1 and in group receiving cisplatin on day 1-2 or 1-3. The difference was also not significant ($p > 0.05$) (Table 4).

## Discussion

The present study suggested that combination therapy of liposomal paclitaxel and cisplatin is effective as NACT before surgery in patients with locally advanced cervical cancer. The toxicities are controllable.

In the literature, several regimens have been reported to be effective against locally advanced cervical cancer in the NACT setting with a response rate of 78% - 95% [5]. Combination therapy of paclitaxel and cisplatin is one of the effective regimens reported. The response rate is usually 72% - 90% [20-22]. In one study, paclitaxel and cisplatin regimen was given to 43 patients with Stage IB2 to IIB cervical cancer before surgery. Paclitaxel 60 mg/m$^2$ was administered intravenously over three hours, followed by cisplatin 60 mg/m$^2$, also administered intravenously. The chemotherapy was administered every ten days and for three courses. The total response rate was 90.7% (39/43), including a complete response rate of 39.5% (17/43) and a partial response of 51.2% (22/43). Stable disease occurred in 9.3% (4/43) of patients [22].

There is only limited report on the use of liposomal paclitaxel in cervical cancer. One study compared the efficacy and toxicities of liposomal paclitaxel or paclitaxel combined with cisplatin or carboplatin in concurrent chemoradiotherapy. Both paclitaxel and liposomal paclitaxel was administrated at a dose of 135 mg/m$^2$, cisplatin 80 mg/m$^2$, and carboplatin AUC (area under curve) 4 – 6. Treatment repeated every 21 days for two to three cycles. Radical radiotherapy was given to both groups at the same time. Seventy-one cases were included in paclitaxel group and 91 in paclitaxel liposome group. The overall response rate was 90.1% and 89.0%, in paclitaxel and paclitaxel liposome group, respectively. The one-year cumulative survival rate was 91.4% for paclitaxel group and 89.2% for paclitaxel liposome group. Both overall response rate and one-year cumulative survival rate is not significantly different between two groups [23]. However, in that study, treatment efficacy is the combined result of chemotherapy and radiotherapy. One cannot see the exact effect of chemotherapy.

In the current study, liposomal paclitaxel combined with cisplatin was given to patients with locally advanced cervical cancer as NACT. The overall response rate was 86.1% (62/72), including a CR rate of 27.8% (20/72), and a PR rate of 58.3% (42/72). The response rate in the present study was similar to that (72% - 90%) of paclitaxel combined with cisplatin reported in the literature [20-22]. The pathological CR rate was 13.9% (10/72) in the current study, which was close to that (11% -20%) reported in the NACT of locally advanced cervical cancer by cisplatin or carboplatin based regimens in the literature [5]. Pathological CR after NACT or chemoradiotherapy was shown to be associated with favorable prognosis [24, 25].

The toxicities of conventional paclitaxel were mainly hematological toxicities, neuropathy, and hypersensitivity reactions. The latter two adverse effects were caused by the dehydrated ethanol and polyethoxylated castor oil (Cremophor EL) used to dissolve paclitaxel [6]. Liposomal paclitaxel is designed to not only obviate the hypersensitivity reactions associated with the Cremophor EL vehicle, but also decrease the toxicities that arise from the drug's pharmacological action [9, 26]. A reduction in toxicities leads to a substantial elevation of the maximum tolerated dose [26]. Several clinical trials showed that liposomal paclitaxel has less hypersensitivity reactions and neuropathy, and similar other toxicities, such as hematological toxicities, when compared to paclitaxel [13-15,23]. In one prospective study, liposomal paclitaxel or paclitaxel plus cisplatin regimen was given to a total of 100 patients with non-small cell lung cancer. Liposomal paclitaxel or paclitaxel was administrated at a dose of 150 mg/m$^2$, and cisplatin 75 mg/m$^2$ every 21 days. There was no significant difference as of grades 3 and 4 toxicity including hematological toxicities and nausea/vomiting between the two arms. Peripheral neuropathy occurred less frequently in the liposomal paclitaxel plus cisplatin group than in the paclitaxel plus cisplatin group (8% vs. 28%) [15].

In the current study, liposomal paclitaxel was administered at a dose of 175 mg/m$^2$, and cisplatin 75 mg/m$^2$. The toxicities were generally controllable. Hematological toxicities were the major dose-limiting toxicities. Grade 3/4 anemia and neutropenia was observed in 6.9% and 18.1% patients, respectively. No grade 3/4 thrombocytopenia happened. Other frequent adverse effects were vomiting and alopecia, which was 58.3% and 65.3%, respectively. Peripheral neuropathy occurred in 6.9% patients, all were grade 1. No allergy reaction was noted.

One of the major adverse effects of cisplatin is renal impairment. Administering the total dose of cisplatin per cycle dividedly may decrease the impact of cisplatin on renal function. In this study, the impact of different method of cisplatin infusion on CrCl was evaluated by comparing the CrCl decrease after two cycles of chemotherapy. CrCl decrease of $\geq$ 10 ml/min occurred in 53.8% (7/13) and 37.3% (22/59) patients, and CrCl decrease of $\geq$ 20 ml/min in 30.7% (4/13) and 18.6% (11/59) patients, respectively, in group receiving total dose of cisplatin on day 1 and in group receiving divided dose of cisplatin on days 1–2 or 1–3. Although the difference was not significant, the tendency indicated that the group receiving total dose of cisplatin on day 1 may suffer more renal impairment than the group receiving cisplatin dividedly on days 1-2 or 1-3.

Dividing the total dose of cisplatin per cycle to two or three doses and administering on days 1-2 or 3 may decrease renal toxicities, but may also compromise the antitumor effects. In this study, the response rate was 84.6%, 88.2%, and 84.0% in patients with total dose of cisplatin per cycle administered on day 1, or dividedly given on days 1–2, or on days 1–3, respectively. It seems that the response rate in different group was close.

One should be aware of the limitations of this study. This is a retrospective study and is subject to the limitations of this type of study. The number of cases is small. The results were from one center. Thus, the interpretation of the results should be made with caution.

In conclusion, the study findings support further evaluation of liposomal paclitaxel with cisplatin as an additional chemotherapy regimen which may be efficacious and tolerable in the NACT of cervical cancer.

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