A phase II study of weekly paclitaxel and cisplatin followed by radical hysterectomy in stages IB2 and IIA2 cervical cancer

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On behalf of

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Background-1

- **FIGO stage IB2 or IIA2 cervical carcinomas (CC) are associated with a higher incidence of nodal metastases as well as central, regional, and distant recurrences compared with smaller tumors.**
- **It is generally accepted that radical surgery or radiotherapy can be curative for the majority of patients with early-stage CC.**
- **Concurrent chemoradiation (CRT) is the standard treatment for locally advanced CC.**

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Background-2

- The 5-year survival rates of FIGO stage IB2 and IIA2 are around 70-75% according to the 2006 FIGO annual report. The treatment of such patients remains controversial.
- Neoadjuvant chemotherapy (NAC) has been utilized in cervical cancer for more than two decades.
- Sardi et al proposed a "quick" chemotherapy regimen (cisplatin, vincristine, and bleomycin (POB) at 10-day intervals) which attained a satisfactory tumor size reduction.

Background-3

- **The efficacy of POB regimen was confirmed on FIGO stage IB and IIA bulky CC before radical hysterectomy and pelvic lymph node dissection (RH-PLND) in CGMH.** ***Lai et 1997; Huang et al. 2003; Chang et al. 2000***
- **Patients with adeno-adenosquamous carcinoma and age younger than 35 years had significantly worse outcomes .** ***Lai et 1997***
- **There was no difference in recurrence-free or overall survival (RFS or OS) for NAC plus radical surgery as compared with RT alone in a phase III RCT.** ***Chang et al. 2000***

Background-4

- Park et al. reported 90.7% response rate and PLN positive rate of 7% using palcitaxel (60 mg/m^2) and cisplatin (60 mg/m^2) of 10-day intervals. More importantly, the toxicity was relatively low.
- A phase I dose-escalation trial using 7-day schedule and paclitaxel (50-80 mg/m^2) and cisplatin (fixed 40 mg/m^2) of 3 cycles for stages IB2-IIA2 SCC was well tolerated without interfering the following surgical treatment. *(Chou, et al. Am J Clin Oncol 2017; 40:241-249.)*

Results of phase I

- **No DLT occurred. Twelve subjects were enrolled without reaching maximum tolerated dose, nor was any RH-PLND procedure delayed for >2 weeks.**
- **Pathological response rate was 50% (complete in 2, optimal partial in 1, modest partial in 3).**
- **Paclitaxel dose level seemed unrelated to pathological response.**

Chou, et al. Am J Clin Oncol 2017; 40:241-249.

Pathological response

- Pathological complete response (pCR): if there was completely absence of cancer cells found in cervix or any surgical specimens without new lesions by imaging
- Pathological optimal partial response (poPR): if only microscopic tumor present with cervical **stromal invasion < 1/3**
- Pathological modest partial response (pmPR): if stromal invasion > 1/3 without those definitions of stable disease
- Pathological stable disease (pSD): if full thickness cervical stromal invasion, stromal invasion > 2/3 with lymphovascular space invasion, PLN metastasis or parametrial extension
- Pathological progressive disease (pPD: if tumor size larger than 25% increase or new lesions were found. PET response of Response Evaluation Criteria for Solid Tumor (RECIST) 1.1 can be used for defining progression.

Results of phase I

- No subjects had ≥ grade 3 acute adverse events.
- Seven patients (58.3%) received postoperative radiotherapy or chemoradiation (RT/CRT).
- Patients with HPV16-negative tumor and age ≥ 55 years had higher risk (100%) of adjuvant RT/CRT after NAC.
- With a median follow-up of 45.5 months, all 12 patients remained alive without disease.
- Selecting patient age <55 years or HPV16-positive and NAC of 4 to 5 cycles may reduce postoperative RT/CRT in future phase II or III trials.

Chou, et al. Am J Clin Oncol 2017; 40:241-249.

Study design and objectives

- **Study Design**

Multicenter phase II study, with Simon's 2-stage design

- **Primary objective:**

Postoperative RT/CRT rate

- **Secondary objectives:**

1. **Overall survival and safety**
2. **Progression-free survival**
3. **Response rate**
4. **To assess Quality-of-Life**

Inclusion criteria-1

- HPV16+ aged 35-70 years, HPV16-negative aged 35-55 years
- (1) untreated, histologically confirmed SCC of the uterine cervix
- (2) FIGO stage IB2 or IIA2, with tumor extension limited to within the upper one third of the vaginal wall. Bulky tumor is defined as (a) a cervical tumor with the largest diameter >4 cm or (b) a cervix tumor size verified by magnetic resonance image (MRI) or 3-dimensional (D) computed tomography (CT)

Inclusion criteria-2

- (4) adequate marrow, liver and renal functions
- (5) adequate cardiopulmonary function that tolerates radical hysterectomy
- (6) Eastern Cooperative Oncology Group performance status of 0 to 2
- (7) had written informed consent to participate in the study

Exclusion criteria-1

- (1) adenocarcinoma, adenosquamous carcinoma, or small cell carcinoma
- (2) histological or cytological documented extrapelvic metastasis (pelvic LN+ is eligible)
- (3) concurrent or history of malignant tumor(s) other than treated nonmelanoma skin cancer

Exclusion criteria-2

- (4) had undergone surgical procedure other than cervical biopsy/conization or had received cytotoxic procedure(s) including chemotherapy, radiotherapy (RT) or treatment with biologic response modifier(s) for the cervical cancer
- (5) participate in other investigational treatments
- (6) history of allergic reaction to platinum or paclitaxel
- (7) uncontrolled intercurrent illness; (8) pregnant or breast feeding women

Treatment

- Stage 1: Paclitaxel (60 mg/m^2) and cisplatin (40 mg/m^2) , 7-day cycle, 5 courses followed by RH-PLND, if G3/4< 30%, proceed to stage II, If G3/4>= 30%, reduce to 4 courses
- Postoperative adjuvant therapy was tailored according to pathological response. Generally, patients with PLN or parametrial metastasis would receive CRT. RT was offered for positive surgical margins or pSD without extra-cervical spread

Simon's 2-stage design

- **Stage 1: Paclitaxel (60 mg/m^2) and cisplatin (40 mg/m^2) , 7-day cycle, 5 courses followed by RH-PLND**
- **If G3/4< 30%, proceed to stage II, If G3/4>= 30%, reduce to 4 courses**

SAMPLE SIZE

- **The primary objective is to determinate the proportion of subjects with pathological modest partial response (pmPR) stable disease (SD) or progressive disease (PD), while the difference in 5-year survival rate of subjects with NAC+RH-PLND compared with standard CCRT will be the secondary objectives.**
- **Based on the pilot research, 58.3% (pmPR+SD+PD) had to receive post-operative RT after 3 courses of NAC and RH-PLND. We hypothesize that with 5 courses of NAC, the expected pmPR+SD+PD rate could be 25 ±5%.**

SAMPLE SIZE

- Based on the pilot research, a sample size of 51 Subjects is required for predicting a 25 ±5% of post-operative RT/CRT after 5 courses of NAC with an 80% power at a significance level 0.05.
- According to 10-20% loss expected, 56-62 subjects will be enrolled in this study.

SAMPLE SIZE

- **According to G3/4 AE of <30% (desirable level) for stage 1 and we expect to achieve at significance level 0.05 and 85% power, it gives (r1/n1, r/n)=(6/26, 13/51). In other words, at stage 1, 26 subjects will be enrolled in order to achieving an 85% power at a significance level 0.05. If more than 6 have G3/4, then decrease courses of NAC to 4 and complete the 51 evaluable patients.**

18

Funding and length of study

- **Paclitaxel may not be reimbursed by the national insurance policy, for example Taiwan, therefore it will be provided by the funding of each principal investigator of each country.**
- **Dr. CH Lai has provided initiating funding from MDOHW105(6)-TDU-212-113003 for the Taiwanese sites, and Dr. HJ Huang has applied CPRPG from Chang Gung Medical Foundation. Dr. Hextan Ngan is submitting IRB and hospital intramural grant for the Hong Kong site.**
- **LENGTH OF STUDY: 5 years accrual plus 3 years follow-up (02/2015-12/2023)**
- **First patient enrolled: May 2016**
- **Last patient enrolled: Dec 2020**