Concurrent Radiotherapy, Paclitaxel and Dose Escalating Carboplatin in the Treatment of Cervical Cancer – A Phase I Study

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Abstract. *Background: Concurrent radiation therapy (RT) and chemotherapy represents the standard treatment of locally advanced cervical cancer. This study was designed to determine the feasibility and toxicity of concomitant administration of RT with twice per week paclitaxel and carboplatin. Materials and Methods: Nine women with cervical cancer stage IB2-IVA were treated with standard RT and twice per week paclitaxel at a dose of 30 mg/m^2 with carboplatin in escalating doses starting at an AUC of 5. Results: One out of the four patients who received carboplatin at AUC 5 developed grade III toxicity according to the National Cancer Institute (NCI) grading system. Two out of the five patients who received carboplatin at AUC 6 developed grade III toxicity. A clinical response was achieved in 8 patients (89%), with a complete response (CR) in 5 patients (56%). Conclusion: Combining RT with twice weekly paclitaxel (30 mg/m^2) and carboplatin (AUC of 6) is a tolerated regimen, active in controlling locally advanced cervical cancer*

Worldwide, cervical cancer remains a major health problem and is one of the leading causes of cancer death in developing countries. Early-stage tumors can be managed with either surgery or radiation therapy (RT) with equally good results (21). For locally advanced cervical cancer platinum-based chemotherapy has been added to radiation treatment on the basis of the results of five randomized trials demonstrating improved local control, overall and disease-free survival with chemoradiotherapy (1-6). Two meta-analyses of published trials performed by researchers from Canada and the UK confirmed the significant benefit of concomitant administration of platinum chemotherapy and radiation (7, 8). The improvement in outcome has, however been, accompanied by increased acute toxicity, specifically of hematological and gastrointestinal type.

In an effort to improve the therapeutic ratio, additional chemotherapeutic agents such as carboplatin and paclitaxel have been tested clinically.

Carboplatin is a radiosensitizing alkylating agent (23, 24) with similar efficacy to cisplatin and less nephro- and neurotoxicity and less emesis (20). Phase I studies involving patients with cervical cancer stages IB-IVA treated with concomitant RT and weekly carboplatin achieved overall response rates of 80% with good tolerance of the regimen (9-11).

Paclitaxel, a naturally occurring taxane that potentiates radiation-induced damage by accumulation of cells in the G2/M phase of the cell cycle (19, 22) produced complete clinical response rates ranging between 17 and 93% in phase I studies. One third of the patients experienced grade 3 and higher toxicity, mainly hematological and neurological (12-14).

Combining both paclitaxel and carboplatin with definitive RT produced a clinical response in more than 80% of patients, with grade 3-4 gastrointestinal and hematological toxicity in the range of 9 to 50% (15-18).

Inspired by prior experience in locally advanced cervical and breast cancer (25), a phase I study was initiated at New York University to determine the feasibility and toxicity of treating newly diagnosed cervical cancer patients with locally advanced disease (stages IB2 to IVA) with concomitant twice a week paclitaxel and carboplatin with concurrent RT.

Carboplatin was administered in increasing doses to groups of three enrolled patients while the paclitaxel dose was kept constant. The objectives consisted of the determination of the maximum tolerable dose (MTD) of carboplatin when given twice per week with paclitaxel and evaluation of clinical efficacy (tumor response) of this regimen. The rationale of biweekly administration of both paclitaxel and carboplatin was based on *in vitro* experiments

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Key Words: Cervical cancer, carboplatin, paclitaxel, concurrent radiotherapy.

and clinical data showing that prolonged exposure to the drugs at lower doses gave not only persistent cytotoxic but also radiosensitizing effects with lower toxicity than conventional regimens (26).

Materials and Methods

Patients were considered eligible for enrollment if they were 18 years of age or older, had histologically confirmed previously untreated primary cervical carcinoma (squamous, adeno-, or adenosquamous), International Federation of Gynecology and Obstetrics (FIGO) stages IB2 to IVA, Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2 and negative paraaortic lymph nodes determined by imaging studies or-if radiographically positive, biopsy-proven negative histology. A negative serum pregnancy test was required prior to enrollment and the treatment to be started no more than 8 weeks after the conclusion of staging.

The laboratory criteria for entry included a neutrophil count equal to or greater than 3,000/ml, platelets count equal to or greater than 100,000/ml, creatinine level less than 2.0 mg/dl, bilirubin level less than 1.5 times normal and liver enzyme levels less than 3 times normal.

Patients were ineligible if the cervical tumor was a recurrence or if they had received prior pelvic RT, had a history of previous or concomitant other malignancies, except for nonmelanoma skin carcinomas and breast ductal carcinoma *in situ*, were HIV positive or had had previous partial hysterectomy.

Pretreatment evaluation included history, physical examination, hematological and serum chemistry studies and chest radiography. A CT scan of the abdomen and pelvis was obtained. Cystoscopy and proctoscopy were performed at the discretion of the gynecological oncologist, when clinically indicated.

All the patients received a combination of external beam RT (EBRT) and brachytherapy (BT). EBRT was administered to the entire pelvis for a dose of 4500 cGy in 25 fractions, five days per week, for 5 weeks, concomitant with systemic chemotherapy. The radiation source was a linear accelerator, the energy used was 10 and 18 MV, at a treatment distance of 100 cm. All the patients underwent CT scan-based simulation. The radiation ports consisted of a four- (anterior, posterior, right and left lateral fields) or two-field arrangement (anterior and posterior ports) extending from L4-L5 interspace to at least 3 cm inferior to the lowest extension of the tumor, or at the lower border of the obturator foramen, whichever was more inferior. The lateral fields were shaped to cover the presacral lymph nodes, uterosacral ligaments, external, common iliac lymph nodes, the entire uterus and the tumor with 3 cm margins. All the fields were treated each day. EBRT was followed by intracavitary BT administered with a Fletcher applicator (tandem and 2 colpostats). The first three patients enrolled received low dose rate BT delivered using ^{137}Cs in one or two insertions. The last six patients were treated with high dose rate/ ^{192}Ir as the source for total of four fractions. The cumulative point A dose ranged between 65 Gy and 89.50 Gy (median 84 Gy). The dose to the rectum and urinary bladder was kept below 66 Gy and 70 Gy respectively. The total treatment time to complete the entire course of radiation therapy ranged from 44 to 60 days (median 53 days).

The systemic treatment was administered twice weekly (Monday and Thursday, or Tuesday and Friday) during the 5-week external radiation therapy (five one-week chemotherapy cycles) and was not given during brachytherapy. It consisted of paclitaxel at a dose of 30 mg/m^2 administered over 1 hour with standard premedication followed by carboplatin in escalating doses starting at an area under the cure (AUC) of 5. The study was designed to enroll patients in groups of three per dose level of carboplatin with dose increments of AUC 1 until either an AUC of 10 or MTD was achieved. The carboplatin dose was calculated according to the Calvert formula:

$$\text{Total carboplatin dose (mg)} = \text{AUC (of the target dose level)} \times (\text{glomerular filtration rate} + 25).$$

The patients were evaluated weekly for disease response and toxicity, symptoms were assessed, physical examination and blood testing were performed. Adverse effects were graded according to National Cancer Institute (NCI) criteria. Hypersensitivity reactions were recorded as adverse events. Dose limiting toxicity (DLT) was defined as grade 4 neutropenia, grade 4 thrombocytopenia or grade 3-4 non-hematological toxicity lasting more than 5 days.

The response after the entire course of treatment was evaluated by pelvic examination within the first month of therapy completion. CT scans of the abdomen and pelvis were obtained for five patients within 3 months of the completion of therapy. Complete response (CR) was defined as symptom-free and disappearance of all clinical evidence of tumor. Partial response (PR) was defined as 50% or greater decrease in cervical lesions and improvement in patient's symptoms. Progressive disease was defined as an increase of more than 25% of any measured lesion or the appearance of metastatic lesions.

Results

Nine patients with newly diagnosed biopsy-proven, locally advanced squamous cell carcinoma (two IB2, six IIB, one IIIB) were enrolled in this study. For each patient, an Institutional Review Board (IRB)-approved informed consent was obtained. Three patients were Hispanic, one Caucasian and five of Asian background. The median age was 48 years, ranging from 24 to 68 years. The first four patients enrolled were treated with carboplatin at an AUC of 5. None developed DLT and the next five patients were entered at an AUC level of 6.

Two patients in the AUC 6 group developed DLT (Tables I and II). Subsequently, AUC of 6 was considered the MTD. Four patients developed an allergic reaction during paclitaxel infusion that was reported as grade 2.

Eight out of the nine enrolled patients achieved an objective clinical response (89%) and five had a CR (56%). One patient (11%) had significant persistent local disease at the completion of the entire course of chemotherapy and radiotherapy (stable disease), as indicated by physical examination and CT scan with contrast of the pelvis.

Conclusion

The results of our pilot study are in agreement with similar published data for cervical cancer and other malignancies which showed that combining concomitant

Table I. *Chemotherapy administration and maximum toxicity.*

Dose level	No. of patients entered per AUC level	No. of patients that received all 5 cycles according to the Protocol	Comments	Maximum toxicity
Carboplatin at AUC 5 + Paclitaxel 30 mg/m^2	4	3	First patient enrolled in this group received 3 cycles and refused further participation.	One patient who completed the entire chemotherapy course developed grade III gastrointestinal side-effects (diarrhea), not considered DLT due to very brief duration of symptoms.
Carboplatin at AUC 6 + Paclitaxel 30 mg/m^2	5	4	1 patient enrolled in this group received 3 cycles and refused further participation.	One patient developed grade III dermatological, hematological toxicity and fatigue, that met criteria for DLT. A second patient developed grade III diarrhea, that fulfilled criteria for DLT.

carboplatin and paclitaxel during pelvic radiotherapy is tolerable and effective. Carboplatin at an AUC level of 6 was found to be the MTD for this dose-dense regimen that administers chemotherapy twice per week for 5 weeks with a paclitaxel dose of 30 mg/m^2. Acute hematological and gastrointestinal toxicities were the most frequently encountered and dose-limiting side-effects. Tumor response was found in the majority of patients (89%), with a rate similar to published reports involving similar chemotherapeutic combination.

The administration of carboplatin and paclitaxel according to the regimen used in this study is well tolerated with manageable toxicity. This combination is active in controlling locally advanced cervical cancer when administered with external beam radiation.

Table II. *Number of patients developing acute toxicity. For each patient, the highest grade of each toxicity is reported.*

Toxicity	Grade 1	2	3	4
Leukopenia	1	1	0	0
Platelets	0	1	0	0
Anemia	2	1	1	0
Nausea	2	0	0	0
Vomiting	2	0	0	0
Diarrhea	2	0	2	0
Genitourinary	1	0	0	0
Cardiovascular	0	0	1(DVT+PE)*	0
Neurological	1	0	0	0
Allergy	0	4 (Paclitaxel-related)	0	0
Dermatological	1	0	1	0
Fatigue	0	0	1	0

*DVT: Deep venous thrombosis; PE: Pulmonary embolism. This event was not related to chemotherapy; it occurred after chemotherapy was completed and during brachytherapy secondary to prolonged immobilization.

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Received April 16, 2008
Revised June 8, 2008
Accepted June 16, 2008