Original Article-II

Chemoradiation in Locally Advanced Cervical Cancer : A Randomized Trial

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ABSTRACT

Background: **Radiation with concurrent chemotherapy (weekly cisplatin) is currently standard of care for locally advanced cervical cancer. Gemcitabine, a pyrimidine analogue is a potentially radio-sensitizing drug. We compared cisplatin and gemcitabine in the treatment of locally advanced cervical cancer.**

Methods: **90 patients with locally advanced squamous cell cancer of the cervix (stage IIB-IVA) were randomized to receive either cisplatin 40mg/m^2 weekly or gemcitabine 150 mg/m^2 weekly (45 patients in each arm) along with external beam radiation (50Gy in 25# over 5 weeks). This was followed by three insertions of high dose radiation (HDR) intracavitary brachytherapy one week apart.**

Results: **At a median follow up of 13months, 25 (55.56%) patients were in complete response (CR) in the cisplatin arm compared to 22 patients (48.89%) [p=0.67] in gemcitabine arm. 10 patients (22.22%) in cisplatin arm had either died or lost to follow up compared to 11 patients in gemcitabine (24.44%) arm. Nausea/vomiting was higher in cisplatin arm. Diarrhea, skin reaction and hematological toxicity were more in gemcitabine arm.**

Conclusion: **Cisplatin seems to be a better option than gemcitabine when used concurrently with radiation for locally advanced cervical cancer both in terms of response and toxicity.**

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INTRODUCTION

Cancer of the cervix is a common cancer among women worldwide. For locally advanced disease (FIGO stage IIB-IVA), concurrent chemoradiotherapy is currently standard of care.[1] Theoretically, chemotherapy may act synergistically with radiotherapy by inhibiting the repair of radiation induced damage, promoting the synchronization of cells in 'S' phase of the cell cycle, initiating proliferation in non-proliferating cells and reducing the fraction of hypoxic cells that are resistant to radiation. Various drugs e.g. hydroxyurea, mitomycin, 5-fluorouracil, cisplatin and paclitaxel have been used alone or in combination. Cisplatin is most widely used.[2]

Gemcitabine (2deoxy 2'-2' difluoro-cytidine) is a novel deoxycytidine analogue is a cell cycle specific (S-phase) cytotoxic agent that kills the cells in S-phase undergoing DNA synthesis. It also blocks cells through G /S phase boundary. Mc Cormack et al used gemcitabine[1] with radiation in patients with locally advanced cervical cancer and concluded that gemcitabine is a more potent radiosensitizer than cisplatin.[3]

In present study, we studied role of radiation with concurrent weekly cisplatin or gemcitabine in locally advanced cervical cancer.

PATIENTS AND METHODS

90 patients with histologically proven locally advanced (stage IIB-IVA) squamous cell cancer of the cervix were treated from January 2006 to March 2007. Evaluation included- detailed physical examination including pelvic examination, chest X ray and intravenous pyelography (IVP) and cystoscopy and

proctosigmoidoscopy to determine the clinical stage of cancer. Patients with poor performance status (KPS< 70%) were not included. Patients were eligible if they had Hb level > 10gm/dl, WBC count > 4000/mm^3, platelet count > 1, 00,000/mm^3, normal renal (serum creatinine < 1.2mg %) and hepatic function (serum bilirubin < 1mg %). Prior to randomization, patients were informed about the treatment options and written informed consent was obtained.

Treatment Protocol: Patients were randomized into control arm (45 patients) and trial arm (45 patients). Randomization was carried out by a permuted block arrangement. In the control arm, patients received weekly cisplatin 40 mg/m^2 intravenously × 5 weekly doses concurrently with external beam radiation (EBRT). Patients in the study arm received weekly gemcitabine 150mg/m^2 concurrently with EBRT for 5 cycles.

Chemotherapy: Chemotherapy was administered weekly. It was administered as per standard guidelines 2 hours before RT. In Arm 2, gemcitabine was diluted in 250 mL of normal saline and given iv over 30 min. Antiemetic prophylaxis consisted of 8 mg of dexamethasone and 8 mg of ondansetron given intra venously.

Treatment with cisplatin and gemcitabine was withheld if WBC count dropped below 2500/mm^3 or platelet count dropped below 50000/mm^3 and it was resumed once the counts rose above these levels.

Radiotherapy: EBRT was administered to the whole pelvic region using Telecobalt (Theratron 780C) Machine using anteroposterior-posteroanterior portals to a total dose of 50 Gy in 25 fractions over 5 weeks. The field margins were:

- Superior border: At the level of L3-L4 vertebral interspace.
- Inferior border: At the level of lower border of symphysis pubis or up to the level of introitus, if there was vaginal involvement.
- Lateral border: A 2cm margin lateral to the bony pelvic wall

Patients were treated using the SAD (source-axis distance being 80 cm) method. Both the portals were treated daily and dose was calculated at the midplane. It was followed by three insertions of HDR-intracavitary brachytherapy (ICBT) delivering 7Gy/# one week apart. The total dose delivered to Point A was 80 Gy. Treatment was completed within 8 weeks in all patients, except in 4 patients in the gemcitabine arm due to low WBC counts and radiation was temporarily stopped and treated with G-CSF. 2 patients in each arm needed blood transfusion due to anemia (Hb < 9gm %). In them the total treatment time prolonged to 9-9.5 weeks.

Response Assessment: All patients were assessed on the basis of symptomatic and clinical improvement. Response was graded according to WHO response criteria. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC). Patients were reviewed weekly during chemoradiation and after completion of treatment, every month for the first 3 months and every 3 months thereafter.

RESULTS

Patient Characterestics: Patients median age was 52 years, ranging from 34 to 68 years. Patients characteristics are shown in Table 1. There were no significant differences between the two groups. Patients who suffered from treatment related toxicities were offered gap in treatment but all the patients completed treatment within 10 weeks. Median follow up is 13 months ranging from 0.7 months to 23.8 months. Data has been censored on 31st May 2008.

Response: All patients were evaluable for response and toxicity. Response was evaluated 6 weeks after the completion of treatment. 75% of patients achieved complete response in the cisplatin arm compared to 69% in the gemcitabine arm, p=0.64.

At a median follow up of 13 months period, 25/45 patients (55.56%) in cisplatin arm were in continuos CR compared to 22/45 patients (49%) in gemcitabine [p= 0.67]. 7/45 (15.55%) and 3/45 (6.67%) patients were lost to follow up and

Table 1: Patients' Characterstics

Sr. No.	Characteristics		RT+cDDP [n= 45]	RT+Gem [n= 45]
1.	Age Group (Yrs)	31- 40	3	2
		41-50	23	25
		51-60	15	16
		61-70	4	2
2.	Parity	1	5	4
		2	11	12
		3	13	15
		4	12	9
		5	3	3
		>5	1	2
3.	FIGO Stage	IIB	13	15
		IIIA	3	2
		IIIB	27	25
		IVA	2	3

RT= Radiotherapy, CDDP= Cisplatin, Gem= Gemcitabine, n= no. of patients

died respectively in cisplatin arm compared to 6/45 (13.33%) and 5/45 (11.11%) patients, respectively in gemcitabine arm. (Table 2)

Toxicity: Toxicities were graded according to NCI-CTC (version 2). There were no treatment related deaths. The types and frequency of adverse effects are shown in *Table 3.* The frequencies of grade 2 and grade 3 dermatitis were higher in gemcitabine arm (80.8% vs. 64.44%, p = 0.37). Similarly grade 2 and grade 3 diarrhoea was higher in patients receiving gemcitabine (84.44% vs. 62.22%, p = 0.19). Grade 3 hematological toxicity, specially neutropenia and thrombocytopenia were higher in patients receiving gemcitabine (13.33% vs. 6.67%, p = 0.48). Nausea and vomiting were higher in patients in cisplatin arm (grade 2 and grade 3 80% vs. 44.44%, p= 0.08). There was no grade 4 toxicity.

DISCUSSION

Since the 1980s, many phase I-II studies have established that treatment with cisplatin, 5-fluorouracil and mitomycin can safely be combined with pelvic radiation in cervical cancer.[4-6] Since the rate of complete response expected with the use of radiation therapy alone is high, whether there is any incremental benefit from the added chemotherapy could not be assessed in phase II studies. Answers to these questions came from phase III trials of this strategy. Three large randomized studies by Keys et al[7], Rose et al[1] and Morris et al[8] prompted the National Cancer Institute (NCI) in 1999 to

Table 2: Response Rates

	RT+CDDP [n=45]	RT+ Gem[n=45]	p value
Complete Response (CR)	25	22	0.67
Progressive Disease (PD)	10	12	0.8
Lost to follow up	7	6	0.9
Died	3	5	0.71

RT= Radiotherapy, CDDP= Cisplatin, Gem= Gemcitabine, n= no. of patients

issue a rare clinical announcement that "strong consideration should be given to incorporation of cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer."[9]

Currently available data do not allow conclusions to be drawn as to which drugs or regimens are optimal in the treatment of cervical cancer. Gemcitabine is a cell cycle specific cytotoxic agent that has shown anti-tumor activity against a variety of solid tumour e.g. lung, pancreas, breast and bladder. Recently Hernandez et al have demonstrated the radiosensitizing effect of gemcitabine against cervical cancer cell lines.[10] Pattaranutapern et al have also shown efficacy and feasibility of weekly concurrent gemcitabine with radiation in stage IIIB cervical cancer.[11]

In our study, cisplatin based chemoradiation was found to be more effective (55.56% vs. 48.89% p = 0.67 in terms of complete response after the median follow up period) as compared to gemcitabine based chemoradiation arm. Effectiveness of the treatment modality was judged not only by the response but also by the associated side effects. Nausea and vomiting were higher in patients receiving cisplatin concomitant with radiation (Grade 2 toxicity 55.56% vs. 33.33% p=0.06 and grade 3 toxicity 24.44% vs 11.11% p=0.16). Diarrhoea (Grade 2 toxicity 20% vs. 11.11% p= 0.28), skin reaction and hematological toxicity were higher in patients receiving gemcitabine concomitant with radiation. Though these data are not statistically significant, there is a trend towards more effectiveness in the Cisplatin arm with lesser toxicity other than nausea and vomiting. Increasing accrual of patients in the controlled trial will definitely give us a clearer picture, and it is too early to conclude from our small study at present.

Because gemcitabine synergizes not only radiation but also cisplatin, investigations proceeded to evaluate the combination of cisplatin and gemcitabine concurrent with radiation. Alvarez et al performed a feasibility study utilizing a biweekly regimen of cisplatin at 30mg/m^2 and gemcitabine at 20mg/m^2. This planned scheme proved to be toxic, because the first three patients presented grade 3 or higher hematological toxicity. Regarding the efficacy of this combination, complete response in the 37 evaluable patients was 86%.[12] Zarba et al reported a phase I-II study with the combination to establish the recommended weekly dose of gemcitabine beginning at 75mg/m^2 with 25mg/m^2 increments with standard dose of cisplatin 40mg/m^2 weekly during radiation therapy. At this level, grade 3 toxicity was principally non-hematological and included diarrhoea (21%), mucositis (13%), nausea/vomiting (13%) and skin toxicity (13%). Similar to other studies, complete response rate in the 36 evaluable patients was 89% and at a median follow up of 14 months, 81% of the total study population was disease-free.[13] Duenas-Gonzalez et al. carried out a phase II randomized study

Table 3: Toxicities

	Gr 1	Gr 2	Gr 3	Gr 4
		Nausea & Vomiting		
RT+CDDP [n=45]	9	25	11	0
RT+Gem [n=45]	25	15	5	0
		Diarrhoea		
RT+CDDP [n=45]	17	23	5	0
RT+Gem [n=45]	7	29	9	0
		Skin Reactions		
RT+CDDP [n=45]	16	24	5	0
RT+Gem [n=45]	9	30	6	0
		Hematological Toxicity		
RT+CDDP [n=45]	32	10	3	0
RT+Gem [n=45]	25	14	6	0
		Proctitis		
RT+CDDP [n=45]	26	17	2	0
RT+Gem [n=45]	22	20	3	0
		Cystitis		
RT+CDDP [n=45]	34	11	0	0
RT+Gem [n=45]	37	8	0	0

RT= Radiotherapy, CDDP= Cisplatin, Gem= Gemcitabine, n= no. of patients

comparing cisplatin versus cisplatin plus gemcitabine based chemoradiation in cervical cancer. All 83 patients were studied for toxicity and 80 for response. The complete pathologic response rate in the cisplatin and gemcitabine arm was 55% (95% C.I. 35.5–73%) and 77.5% (95% C.I. 57–90%; $p = 0.0201$). The time to complete external beam radiotherapy also favored the cisplatin arm. The gemcitabine combination produced greater GI and hematologic toxicity.[14]

Umanzor et al. in a phase II trial tried to analyze the efficacy of combined cisplatin (40mg/m^2) and gemcitabine (125mg/m^2) along with radiation in locally advanced cervical carcinoma. Of the 23 enrolled patients (mean age 47 years), 20 completed the treatment and were evaluable for response and safety. The complete response rate was 90% (18/20), and partial response rate was 10% (2 patients with persistent disease after therapy).[15] A comparative analysis of these studies and our study is illustrated in Table 4. It can be well interpreted that gemcitabine is a potent radiosensitizer when used in combination with cisplatin in locally advanced cervical cancer, albeit with increased morbidity. There is still no evidence that gemcitabine alone acts as a better radiosensitizer than cisplatin alone in locally advanced cervical cancer.

To conclude, cisplatin seems to be a better option than gemcitabine when used as concurrent chemoradiation for locally advanced

Table 4: Review of Literature

Study	Stage	Chemotherapy	No. of patients	Complete response (median FU period)
Higgins et al.[16]	IB1-IVA	Carbo+Taxane	22	91%(3 m)
Umanzor et al.[15]	IIA-IIIB	CDDP+Gem	20	80%(12 m)
Duanes-Gonzalez et al.[14]	IB2-IIB	CDDP	40	55% (20 m)
		CDDP+Gem	43	77.5% (20 m)
Present Study	IIB-IVA	CDDP	45	55.56% (13 m)
		Gem	45	48.89% (13 m)

CDDP= Cisplatin, Gem= Gemcitabine, Carbo= Carboplatin, M-months

cervical cancer both in terms of response and toxicities, Gemcitabine as a single agent is less effective and feasible for chemoradiation in locally advanced cervical cancer. It remains to be shown in future trials whether the combination of both cisplatin and gemcitabine with concurrent radiation may prove to be superior to either of the single agent.

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