Original Article

A prospective study of response and toxicity of weekly concurrent chemo-radiation with cisplatin versus paclitaxel in patients with locally advanced carcinoma cervix

Pabitra Das, Anis Bandyopadhyay[1], Swapan Kumar Sikdar[1], Debabrata Mitra[1], Shyamal Kumar Sarkar[1]

Department of Radiotherapy, Nil Ratan Sircar Medical College and Hospital, [1]Department of Radiotherapy, Medical College and Hospital, Kolkata, West Bengal, India

ABSTRACT

Context: Concomitant chemo-radiation (CRT) with weekly cisplatin is the "standard of care" for treatment of advanced cases of carcinoma cervix. Although this standard of care reduces the risk of disease recurrence by as much as 50%, efforts are on for further improvement in response rate and local control. **Aims:** The present trial was planned to compare the response and toxicity of CRT with weekly paclitaxel versus weekly cisplatin in locally advanced carcinoma cervix. **Subjects and Methods:** Biopsy proven cases of squamous cell carcinoma, stage IIB–IIIB were randomized into two Arms. In Arm A, patients received external beam radiotherapy (EBRT) dose of 50 Gy in 25 fractions over 5 weeks with weekly Cis-platinum 40 mg/m^2, whereas in Arm B patients received same EBRT with weekly paclitaxel 35 mg/m^2 for 5 weeks, followed by intracavitary brachytherapy of 7 Gy x3# in both the arms. The primary endpoint was response at 3 months of completion of treatment, and secondary endpoints were to compare toxicity and compliance. **Results:** Thirty-two patients of carcinoma cervix were randomized to concurrent ciplatin arm (Arm A) and thirty patients to the concurrent paclitaxel Arm (Arm B). Most of the patients in both Arms had stage III B disease. Five cycles of weekly concomitant chemotherapy were received by 83.3% in Arm A and 60% in Arm B. 56.25% of patients in Arm A and 46.7% of patients in Arm B completed treatment within 8 weeks. There were statistically significant more Grade 2 and 3 diarrhea Arm B as compared to Arm A ($P = 0.003$). There were no Grade 4 adverse events or deaths. Response assessed at 3 month follow up and showed complete response of 83.33% in Arm A and 73.33% in Arm B ($P = 0.521$). The 18 months progression free survival was 86.6% in the cisplatin Arm as compared to 78.3% in the paclitaxel arm ($P = 0.13$). **Conclusion:** Concurrent paclitaxel with external beam radiation in locally advanced carcinoma cervix produces response comparable to concurrent cisplatin.

Key words: Ca cervix, concurrent chemoradiation, paclitaxel

INTRODUCTION

Carcinoma cervix is the second most common cancer among women worldwide. Developing countries where it is often the most common cancer among women, account for 80% of cases.[1] In India an age-adjusted incidence rate ranges from 19 to 44/100,000 in the registries under the National Cancer Registry Programme.[2] It has been estimated that 100,000 new cases of cancer of the cervix occur in India every year, and 70% or more of these are stage III or higher at diagnosis.[3] Concomitant chemo-radiation (CRT) with weekly cisplatin has become the "standard of care" for treatment of advanced cases of carcinoma cervix.[4] Although, there is diversity in

Address for correspondence: Dr. Anis Bandyopadhyay, Department of Radiotherapy, Medical College and Hospital, 88B College Street, Kolkata, West Bengal, India.
E-mail: anish_b123@yahoo.com

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cisplatin dose and dosing schedules, weekly cisplatin at a dose of 40 mg/m^2 concurrent to radiotherapy (RT) is widely accepted as the standard regimen of CRT because of its convenience, equal effectiveness, and favorable toxicity in comparison to other fluorouracil (5-FU) combined regimens. However, although this standard of care reduces the risk of disease recurrence by as much as 50%,[4] various trials are undertaken in the recent years for further improvement in response rate and local control using various chemotherapeutic agents in the concomitant setting.

Paclitaxel has significant activity in solid tumors, especially epithelial ovarian cancer, lung, and breast cancer.[5-8] When used as neoadjuvant agent in locally advanced carcinoma cervix and in recurrent or metastatic setting, it has showed promising results.[9-11] The present trial was planned to compare the response and toxicity in CRT with weekly paclitaxel versus the standard of weekly cisplatin in locally advanced carcinoma cervix, based on the premise that increased posttherapy response rate and local control would eventually add to the survival benefit.

SUBJECTS AND METHODS

The study accrual period was from November 2009 to October 2010 and follow up period was till May 2012. Ethical clearance was obtained from the Institutional Ethical Committee. Pretreatment evaluation included complete medical history and thorough physical examination, biopsy of the lesion, complete haematological and biochemical profile, chest X-ray posteroanterior (PA) view, ultrasonography of whole abdomen, cystoscopy and proctoscopy as and when indicated, complete urinalysis including biochemical and microbiological when indicated, contrast-enhanced computed tomography (CECT) scan and magnetic resonance imaging (MRI) of abdomen and pelvis if required, cardiological evaluation as and when indicated.

After acquiring informed consent the patients were randomized into Arm A and Arm B. Each group will consist of thirty patients. In Arm A, patients received external beam RT (EBRT) dose of 50 Gy in 25 fractions over 5 weeks (every Monday to Friday) with weekly Cis-platinum 40 mg/m^2 for 5 weeks, after necessary premedications and adequate hydration was given on every Monday during external radiation. In the study Arm B patients received EBRT dose of 50 Gy in 25 fractions over 5 weeks (every Monday to Friday) along with weekly paclitaxel 35 mg/m^2 for 5 weeks with necessary premedications was given on every Monday during external radiation.

Radiotherapy

EBRT was given in Telecobalt machine (Co60), Theratron 780-C (Theratronics International Ltd., Canada). All patients underwent computed tomography (CT) simulation for planning EBRT, followed by treatment planning using ASHA/Pinnacle planning software. Pelvic anteroposterior-PA parallel opposed conventional portals were used if the interfield distance (IFD) was <18 cm and 4 field box techniques was used for a thicker patient with greater interfied distance. Midline shielding was not used. During EBRT, patients were reviewed routinely every week by clinically assessment and complete blood counts noted. A haemoglobin (Hb) >10 g/dl, absolute neutrophil count >2000/mm^3 and platelet count >100,000/mm^3 were maintained by using oral hematinics and transfusions of whole blood/blood components whenever required. Following EBRT, pelvic assessment was performed clinically at the last week of EBRT for geometry, disease response and suitability for intracavitary brachytherapy (ICBT). Those having good geometry and complete or near complete response, then ICBT done within 7 days of completion of EBRT after subsidence of skin reaction. Those having partial response, no response or stable disease or deformed geometry not suitable for ICBT, then fractionated multiple insertions interstitial brachytherapy was done.

Brachytherapy

All patients were planned for three weekly ICBT following EBRT to a dose of 7 Gy to point A by high-dose rate brachytherapy using Varian Gammamed Plus Remote Afterloading machine (Varian, Palo Alto, CA, USA) using Ir192 isotope. Before the procedure started, response assessed. This was repeated during all insertions. All applications were carried out using the Manchester Applicator to assure comparability. All patients underwent CT based treatment planning usingy Varian Eclipse Brachy Vision software, (Varian Inc., Palo Alto, CA, USA). The bladder, rectum and distal part of sigmoid colon, which are considered as organs at risk were contoured. All patients underwent three applications of brachytherapy on consecutive weeks and same application technique, geometry and planning were used to minimize variability in outcome.

Response assessment and follow up

Clinical response assessment was performed after completion of external beam radiation therapy, at the time of final fraction of intracavitary insertion and after 6 weeks of treatment completion. All patients underwent a radiological response assessment using CECT/MRI within 3 months of completion of therapy. Response was assessed using the Response Evaluation Criteria in Solid Tumors.[12] Acute toxicity was recorded weekly during EBRT, and after completion of treatment at first follow up. Toxicity was reported using the NCI Common Terminology for Adverse Events, version 4.0, National Cancer Institute, Bethesda. Initially, patients were followed up after 6 weeks

of completion of treatment and thereafter every 3 months till 2 years. Patients were followed up with detailed physical and gynecological examination per speculum, per vaginal and per rectal, papanicolaou smears (after 6 months) and appropriate blood examinations and/or imaging studies.

Statistical analysis

Microsoft Office Excel (XP) software was used for tabulating and comparing data. SPSS version 16 software (Chicago, Illinois: SPSS Inc. 2006) was used for analysis of data. Results were expressed as rates for categorical data: mean and standard deviation for numerical data. Chi-square test was used for association between two categorical variables and a method of testing the significance of difference between them. A confidence level of 95%, that is, $P < 0.05$ was considered statistically significant. Various covariates were compared between two groups using ANOVA and *t*-test for numerical data and Chi-square test was used for categorical variables. Primary endpoint of the study was to compare response at 3 months of completion of treatment; secondary end points were to compare toxicity and compliance.

RESULTS

Sixty-two consecutive patients of carcinoma of uterine cervix of Federation of Gynecology and Obstetrics (FIGO) stage IIA–IIIB met the inclusion and exclusion criteria were included in the study. Thirty-two patients were randomized to concurrent ciplatin arm (Arm A) and thirty patients to the concurrent paclitaxel Arm (Arm B). The background characteristics of the two groups were similar as shown in Table 1. Age range of this study population was 36–60 years. Majority of the patients in both Arms had FIGO stage IIIB disease. About 70% of patients in both arms had Karnofsky Performance Status of 90 or more. In both arms, majority of the patients belonged to poor socioeconomic class (determined by considering education and per capita monthly family income). Median pretreatment hemoglobin was 10.4 g/dl in Arm A (range 8.4–12 g/dl) and 10 g/dl in Arm B (range 8.9–12 g/dl) ($P = 0.635$). The patients who had low pretreatment Hb level received blood transfusion. Twenty-four patients in Arm A and 23 patients in Arm B received EBRT by 4 field box technique. Five cycles of weekly concomitant chemotherapy were received 83.3% in Arm A and 60% in Arm B, four cycles of Concurrent ChemoRadaiation (CCT) were received 16.7% in Arm A and 33.3% in Arm B and three cycles CCT were received 6.7% in only Arm B. Five cycles and four cycles of CCT received more in patients of Arm A compare to Arm B but statistically not significant ($P = 0.090$). Table 2 shows total duration of time required to complete RT in patients of both Arms. Only 56.25% of patients in Arm A and 46.7% of patients in Arm

Table 1: Background Characteristics comparison between two Arms

	Arm 1 (Concurrent Cisplatin)	Arm 2 (Concurrent Paclitaxel)	*P*
Number of patients (*n*)	32	30	
Median age (years)	51 ±4.5	50±5.5	0.61
Parity			
≤3	20	12	0.16
>3	12	18	
Squamous cell pathology	27	25	0.78
Stage			
II	15	9	0.33
IIIA	2	4	
IIIB	15	17	
Median Tumor size			
A (less than 4 cm)	5	6	0.77
B (more than 4 cm but less than 6 cm)	24	20	
C (more than 6 cm)	3	4	
Positive pelvic lymph nodes	9	11	0.33
KPS			
≤80	9	9	0.57
90	23	21	
Socioeconomic status			
Low	22	27	0.06
Others	10	3	
Pretreatment Hb level (gm/dl)	10.5±0.9	10±0.8	0.68

Table 2: Chemotherapy and radiation therapy treatment parameters

	Arm 1 (Concurrent Cisplatin)	Arm 2 (Concurrent Paclitaxel)	*P*
Number of patients (*n*)	32	30	
Median EBRT dose (in Gy)	50 (48-50)	50 (46-52)	
EBRT Field arrangement			
AP-PA	8	6	0.76
4-Field box	24	24	
Number of cycles of chemotherapy received			
5cycles	28	16	0.01
4 cycles	4	12	
3 cycles or less	0	2	
Total treatment duration			
Within 8 weeks	30	4	0.00
> 8 weeks	2	26	
Number of patients suitable for ICRT	30	26	0.33
Post EBRT response (change in tumour size)			
A (more than 4 cm tumor to less than 2 cm)	12	9	0.47
B (more than 4 cm tumor to clinical complete response)	13	9	
C (less than 4 cm tumor to less than 2 cm or clinical complete response	4	6	
D (no appreciable change in tumor size)	3	6	

B completed treatment within 8 weeks (P = 0.096) due to acute toxicity and four patients in Arm A and five patients in Arm B taken more time for improving intracavitary geometry after EBRT for favoring ICBT. Two patients in the cisplatin Arm as compared to four patients in the paclitaxel arm had interstitial application using Martinez Universal Perenial Interstitial Template for unfavourable geometry even after delaying brachytherapy for 2 weeks after completion of external beam radiation therapy.

Acute dermatological toxicity was mostly Grade 1 and Grade 2, with few Grade 3 found in both Arms. Grade 3 toxicity was slightly more in Arm B (20%) as compared to Arm A but not statistically significant (P = 0.734). Upper gastrointestinal (G.I) toxicities were mostly nausea and vomiting. Nausea and vomiting Grade 2 and 3 were more in Arm A compare to Arm B and was statistically significant (P = 0.002). There were statistically significant more Grade 2 and 3 diarrhea Arm B as compared to Arm A (G2 43.3% vs. 23.3 and G3 30% vs. 10%, P = 0.003). Grade 1 and 2 cystitis were more in Arm B compare to Arm A and both Arms were comparable (P = 0.295). No Grade 3 toxicity was seen. Grade 2 and 3 vaginal mucositis were more in Arm B compare to Arm A but statistically not significant (P = 0.675).

Lower G.I toxicity (proctitis) Grade 1 and 2 were more in Arm B compare to Arm A (G1 in Arm B 26.7% vs. 16.7% in Arm A and G2 in Arm B 30% vs. 20% in Arm A, P = 0.299). No Grade 3 toxicity was seen. Serum creatinine was elevated in both Arms. Grade 1 toxicity was more in Arm A compared to Arm B but statistically not significant (P = 0.301). No Grade 2 and 3 toxicity were seen. Serum creatinine increased probably due to dehydration caused by vomiting, diarrhea, and less intake of water. Grade 2 anemia was in Arm A 10 (33.3%) and in Arm B 11 (36.7%). Grade 3 anemia was in Arm A 1 (3.3%) and 7 (23.3%) in Arm B. Grade 2 and 3 anemia were more in Arm B compared to Arm A but statistically not significant (P = 0.105). Grade 1 neutropenia was more in Arm A compared to Arm B (40% vs. 30%) and Grade 2 neutropenia was more in Arm B compared to Arm A (23.3% vs. 0%) and statistically significant (P = 0.019). No Grade 3 toxicity was seen. Grade 1 and 2 allergic reactions due to chemotherapeutic agents were 2 (6.7%) in Arm A vs. 3 (10%) in Arm B and 0% in Arm A vs. 6 (20%) in Arm B, respectively. Hence, allergic reactions Grade 1 and 2 were more in Arm B compared to Arm A and statistically significant (P = 0.027). There were no Grade 4 adverse events or deaths. All patients completed treatment.

Due to the relatively short follow up period, there was little late toxicity observed. There were marginally higher late rectal toxicities in patients undergoing paclitaxel chemo-radiation than in the standard cispltin Arm (P = NS). However, no Grade 3 toxicities were noted in any patient. No patients in either had late bladder toxicities till the last follow up. More patients in Arm B had fatigue, anorexia, weight loss, and anemia than those on Arm A (P = NS). Although no Grade 3 toxicities were noted in any patient, the constitutional toxicities continued to be higher among patients in Arm B even after 6–8 months after treatment completion. Major skin and/or subcutaneous toxicities were not noted in any patient.

Post-EBRT response was assessed according to the clinically appreciable shrinkage of tumour size and was accordingly divided into groups A, B, C, and D [Table 2]. There was more number of patients who had higher degree of tumor shrinkage (Group A) in the concurrent cisplatin Arm. This, however, did not transform into significantly higher complete response rate. Response assessed at 3 months follow up and showed complete response of 83.33% in Arm A and 73.33% in Arm B; partial response of 13.33% in Arm A and 16.67% in Arm B (P = 0.521). At 6 months follow up, there was complete response in 25 patients (83.33%) of Arm A and in 24 (80%) of Arm B and partial response in 2 (6.67%) in Arm A and 3 (10%) in Arm B patients. Thus Complete response was slightly more in Arm A compare to Arm B and partial response was more in Arm B compared to Arm A but statistically not significant (P = 0.896). The patients were followed up for a median duration of 14 months. The disease free survival, defined as freedom from disease in the pelvis beyond 6 months among responders was 86.6% in the cisplatin arm as compared to 78.3% in the paclitaxel concurrent chemoradiation Arm [Figure 1, P = 0.13, logrank test].

DISCUSSION

There is very scarce literature on the use of weekly paclitaxel concurrently with external beam radiation in direct comparison with the standard regimen of weekly

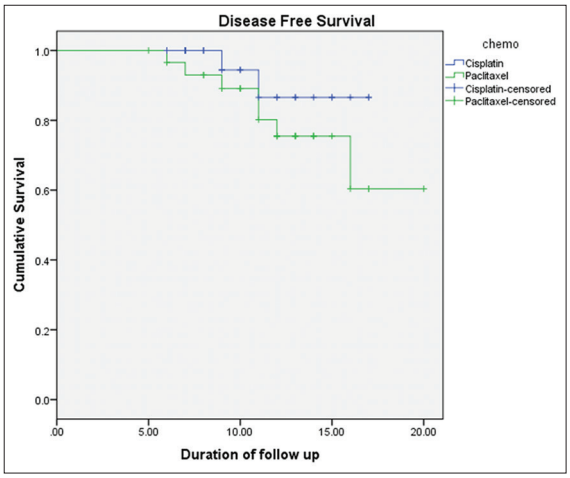

Figure 1: Comparison of disease free survival of the two Arms

cisplatin in advanced carcinoma cervix. The current study was designed with the aim to improve response to concurrent chemotherapy in locally advanced carcinoma of uterine cervix keeping the survival benefit of addition of chemotherapy to radiation intact. The study included were FIGO stage IIA to IIIB and stage IIIB was the most common in both Arms. Since, no patients with obvious para-aortic lymph node metastasis were included and none received extended field RT for para-aortic lymph node, thus allowing for comparability and to on assess the effect of concurrent chemoradiotherapy only on local response.

Previously RT was the only treatment of locally advanced carcinoma cervix but survival rate was not more and the result was quite unsatisfactory. In 1999, National Cancer Institute issued a clinical alert; CRT with weekly Cisplatin has become the "standard of care" for treatment of advanced cases of carcinoma cervix.[13] The updated results of Radiation Therapy Oncology Group (RTOG) 90-01 confirmed that RT with concurrent cisplatin-based chemotherapy should be considered standard treatment locally advanced carcinoma cervix patients.[14] This standard of care reduces the risk of disease recurrence and death by as much as 30%–50%,[15] but attempt continue to find out other drugs with high activity, further improve survival and reduce the risk of disease recurrence. Green *et al*. in their meta-analysis of concurrent chemo-radiation in locally advanced carcinoma cervix, concurrent chemo-radiation improve overall survival (odds ratio [OR]: 0.61: $P < 0.001$) and distant recurrence (OR: 0.57: $P < 0.0001$).[16,17] The absolute survival benefit was 12% and progression free survival benefit was 16% in recent studies. Randomized trials Gynecologic Oncology Group (GOG) and RTOG demonstrated superior results with concurrent chemo-radiation using cisplatin in terms of local control, progression free survival and overall survival in comparison to radiation alone.[18,19]

GOG 120 compared weekly cisplatin with a three drug regimen including cisplatin and 5-FU, the addition of hydroxyurea increased the toxicity of the combination regimen and required compromise in doses of cisplatin and 5-FU. The survival rates were similar in both Arms.[20] Khalil *et al*. showed in their study CRT with weekly cisplatin and paclitaxel provided good local control of disease with different toxicity profile. In the present study, tumor response at 3 month follow up was about 80% in both Arms and did not change much at 6 months follow up also. This is similar to that observed in the Japanese phase I study using both weekly cisplatin (30 mg/m^2) and paclitaxel (50 mg/m^2) with RT. Moreover, there was no significant advantage in response rate in case of paclitaxel regime over cisplatin, in the present study in terms of response after 6 months; although there was more patients with significant tumor shrinkage in the cisplatin Arm.

Recent randomized trials are investigating possible ways to improve further the effectiveness of cisplatin-based chemoradiotherapy regimens without increasing treatment-related morbidity. One of the approaches of this has been use of another cytotoxic drug along with cisplatin. Although use of such a stategy with addition of paclitaxel and gemcitabine along with cisplatin has shown to increase in the 3 years progression free survival this has come at the cost of increased Grade 3 and Grade 4 toxicity.[21-23] Thus, there might be a need for proper selection of a high risk subgroup of patients who might benefit from the use of multiagent concurrent chemotherapy resulting in a increased therapeutic ratio. Retrospective analysis of recurrent and metastatic cervix patients has shown that presence of pelvic lypmhnodes, increased level of serum squamous cell carcinoma antigen after completion of chemoradiotherapy are significantly associated with recurrence/distant failure.[24] Whether these are true risk factors however, needs to be tested in large randomized trials.

Compliance with weekly cisplatin is major concern as the reported range is from 50% to 90%. In several GOG trials, a compliance of about 90% of patients for receiving at least four cycles of weekly cisplatin is reported where as in other smaller trials reported compliance of about 50% for five cycles of cisplatin. Compliance to weekly paclitaxel on the other hand was found to be around 80% in a phase II trial. In our study on the contrary, compliance to ciplatin was better than to paclitaxel (83.3% patients in the cisplatin Arm and 60% patients in paclitaxel Arm completed five cycles of weekly chemotherapy, $P = 0.090$). This may be related to the higher dose of cisplatin administered in the above mentioned studies. While the major limiting acute toxicity in the cisplatin Arm was nausea and vomiting followed by lower G.I toxicity, where as the major limiting toxicity in the paclitaxel Arm was hematological and fatigue, lethargy and in three cases, severe allergic reactions.

The major limitations of this single institutional study were the small sample size and relatively short duration of follow up. So, further accrual of patients with a long-term follow-up should be needed for analysis of long-term toxicity and survival. Moreover, the disease free survival depends on a lot of other factors including brachytherapy dosimetric parameters, which were not considered in this study thus allowing for some degree of bias.

CONCLUSION

Based on the findings of the present study it can be concluded that concurrent paclitaxel with external beam radiation in locally advanced carcinoma cervix produces comparable response to standard treatment of concurrent cisplatin with EBRT with some increased incidence of manageable

acute toxicity. However, whether this ultimately transforms into comparable overall survival and disease free survival needs to be tested in a bigger study with high power and with longer follow up.

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Conflicts of interest
There are no conflicts of interest.

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