Evaluation of Clinical Response and Toxicities of Concurrent Weekly Cisplatin in Comparison to Weekly Paclitaxel with External Beam Radiotherapy in the Treatment of Locally Advanced Cervical Cancer (IIB-IVA)

Abstract

This quasi-experimental study was performed in the Department of Radiotherapy of Dhaka Medical College Hospital, Dhaka for one year period from July 2019 to June 2020. The aim of the study was to evaluate and compare tumor response and toxicities of weekly cisplatin and paclitaxel along with External Beam Radiotherapy in the treatment of locally advanced cervical cancer.Sixty previously untreated female patients with histologically proven locally advanced squamous cell carcinoma of cervix (stage IIB-IVA) were randomized into concurrent chemoradiation with weekly cisplatin and weekly paclitaxel group with thirty patients falling in each group. They were followed up for 3 months at the OPD. Treatment response and toxicities were assessed and compared between two groups. Majority of the patients in both groups were less than 50 years of age. The mean number of chemotherapy cycles was comparable with 90% and 80% of patients receiving 5 doses in arm A & B respectively. Nausea & vomiting were higher in cisplatin group. Diarrhea, allergic reaction, peripheral neuropathy & neutropenia were more in paclitaxel group. There was a complete response rate of 63.3% in cisplatin group and 56.7% paclitaxel group. There were only 3 patients who discontinued treatment (1 in cisplatin group & 2 in paclitaxel group) due to drug-related toxicities. This small prospective study shows that weekly paclitaxel was as effective as weekly cisplatin in concurrent chemoradiation for locally advanced carcinoma of cervix. So, paclitaxel can be used as an alternative to cisplatin in cisplatin contraindicated cases.

Keywords: External Beam Radiotherapy, Locally Advanced Cervical Cancer, Toxicities, Clinical response, Efficacy.

Introduction:

Cervical cancer is the fourth most common cancer among females for both incidence and mortality [1]. The American Cancer Society estimated that, in the United States, in 2017, 12,820 new cases of invasive cervical cancer would be diagnosed and there would be 4,210 deaths due to cervical cancer, representing approximately 1.5% of all cancer deaths in women [2,3].

The disproportionately high burden of advanced carcinoma of cervix in developing countries is largely due to a lack of screening that allows detection of precancerous and early-stage carcinoma of cervix. So, most of the cases are present at more advanced stage, which are inoperable [4].

Concurrent chemo-radiotherapy is the main treatment modality for locally advanced cervical cancer[5]. Chemotherapy may act synergistically with radiotherapy by inhibiting the repair of radiation induced damage, promoting the synchronization of cells in 'S' phase of cell cycle, initiating proliferation in non-proliferating cells and reducing the fraction of hypoxic cells that are resistant to radiation [6].

Paclitaxel, a taxane compound, has high efficacy against solid tumors, especially epithelial ovarian cancer, lung, and breast cancer tumors. Paclitaxel cytotoxicity of human cervical cancer cells has been shown to involve inhibition the Raf-1 kinase activity. Paclitaxel inhibits mitosis by binding tubulin, a structural protein that is necessary for cell division, keeping tumor cells stuck in the G2 and M phases. Paclitaxel also appears to contribute to re-oxidation of hypoxic tumor cells [7].

In our country, patients are diagnosed at an advanced stage in most cases and cisplatin is usually used concurrently with External Beam Radiotherapy[8]. This study was undertaken to compare the use of cisplatin and paclitaxel in concurrent chemo-radiation for locally advanced carcinoma of cervix. This approach would be an effective option for the treatment of cervical cancer.

Material And method

This quasi-experimental study took place in Dhaka Medical College from 01/07/2019 to 30/06/2020. 60 patients with biopsy proven carcinoma of cervix (locally advanced stage IIB – IVA) were enrolled by randomized method. 30 patients were given Cisplatin and another 30 patients were given Paclitaxel. Patients were selected from the radiotherapy outpatient department who met the selection criteria of the study. Data collection was done by semi structured Questionnaire.

Inclusion criteria:

1. Histopathologically diagnosed case of carcinoma of cervix (stage IIB to IVA)
2. No previous history of surgery, chemotherapy or radiotherapy for cervical cancer.
3. Age < 80years.
5. ECOG performance status<=2.
6. Minimum laboratory criteria required to include:
   I. Hemoglobin should be more than 11gm/dl or >60%
   II. Total WBC count>4000/mm3
   III. Total platelet count > 1,00,000/mm3
   IV. Bilirubin level of ≤1mg/dl.
   V. An AST level < 4 times of the upper limit of normal.
   VI. A serum creatinine level of ≤1.5mg/dl.
7. Written informed consent signed prior to enrollment.

B. Exclusion criteria:

1. Patients who were treated with radiotherapy/ chemotherapy or definitive surgery.
2. Evidence of enlarged para-aortic lymph nodes.
3. Hypersensitivity to cisplatin or paclitaxel
4. Distant metastasis
5. Recurrent cases

6. Major vital organ dysfunction
7. Existence of multiple malignancies
8. Eligible patients unwilling to participate in the study
9. Joined in other clinical trial.

List 1 : Figo Staging[9]

Stage	Description
Stage 0	In situ Carcinoma
Stage 1	Similar to localized: confined to organ of origin
Stage II – Stage IV	Extension beyond organ of origin into areas of the pelvis and beyond (regional and distant stages)

Statistical Analysis:

Data was analyzed by using SPSS for Windows v17 software. Continuous data was presented as mean +/- SD while categorical data was presented as frequency and percentage. To see the association between various variables chi-squared test Fisher's Exact test and t-test were used, where applicable. P-value 0.05 or less was considered as significant. Results were presented in tables, figures and diagrams. 95% confidence intervals were calculated for these values.

Result:

Socio-demographic characteristics of respondents

Table 1: Age distribution of the patients (N= 60)

Table 1 below shows the age ranges from 31-70 years. The majority of the patients in both treatment arms (63.3% in cisplatin arm and 56.6% in paclitaxel arm) were less than 50 years. P value was 0.785 which was not significant.

Age (years)	Cisplatin arm	Paclitaxel arm	p-value
31 – 40	4 (13.3)	5 (16.7)	
41 – 50	15 (50.0)	12 (40.0)	
51 – 60	10 (33.4)	11 (36.7)	
61 – 70	1 (3.3)	2 (6.6)	
Mean ±SD	48.40 ± 7.88	49.00 ± 9.03	0.785^{ns}

Table II: Parity of the patients (N=60)

Table II below shows that majority of the patients were muti-para. P value is not significant. Chi-square was done to measure the level of significance. Data were expressed as frequency (percentage).

Parity	Cisplatin arm (frequency%)	Paclitaxel arm (frequency%)	p-value
1.00	3 (10.0)	4 (13.3)	0.439^{ns}
2.00	9 (30.0)	5 (16.7)	
3.00	7 (23.3)	10 (33.3)	
4.00	4 (13.3)	8 (26.7)	
5.00	4 (13.3)	2 (6.7)	
6.00	3 (10.0)	1 (3.3)	
Mean ±SD	3.20 ± 1.52	3.07 ± 1.26	0.712^{ns}

Clinical characteristics of respondents

Figure 1: Distribution of patients according to FIGO staging

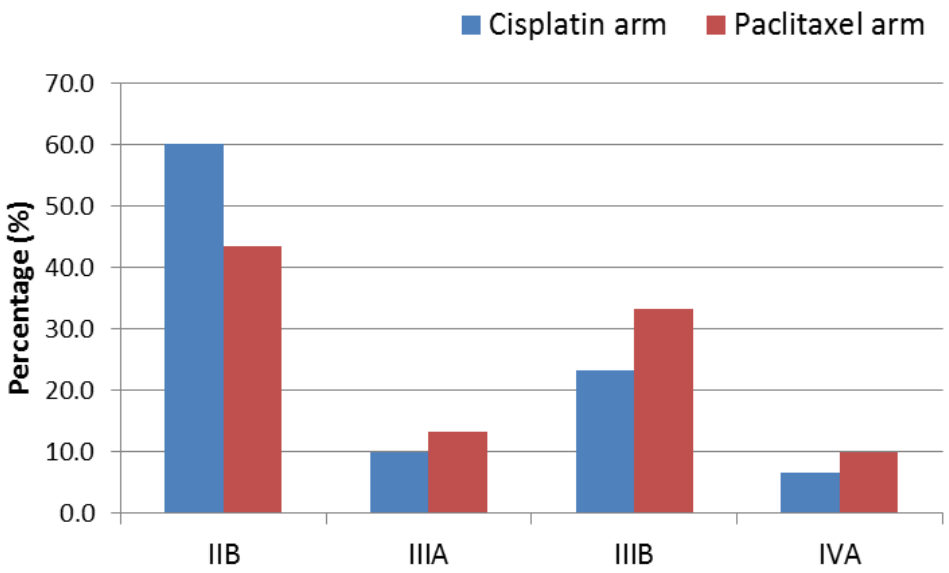

Figure 1 above shows, majority of the patients in the study had stage IIB at diagnosis in both arms (60 vs 43). Chi-Square test was done to measure the level of significance.

Table III: Distribution of the patients by toxicities (N=60)

Table III below shows the treatment toxicities were found to be comparable between the two groups. In the cisplatin group, grade I & II nausea and vomiting were higher in frequencies than paclitaxel group. These differences were statistically significant.

	Grade	Cisplatin arm(frequency%)	Paclitaxel arm(frequency%)	p-value
Nausea/vomiting	Grade I	4 (13.3)	5 (16.7)	0.021[s]
	Grade II	9 (30.0)	2 (6.7)	

	Grade III	3 (10.0)	0 (0.0)	
	Grade IV	0	0	
Diarrhea	Grade I	5 (16.7)	5 (16.7)	0.139[ns]
	Grade II	3 (10.0)	9 (30.0)	
	Grade III	0	0	
	Grade IV	0	0	
Peripheral neuropathy	Grade I	2 (6.7)	10 (33.3)	0.001[s]
	Grade II	1 (3.3)	7 (23.3)	
	Grade III	0	0	
	Grade IV	0	0	
Skin	Grade I	2 (6.7)	6 (20.0)	0.013[s]
	Grade II	0	5(16.7)	
	Grade III	0	0	
	Grade IV	0	0	

*ns= non-significant

S= significant

Figure II: Treatment status of the patients (N=60)

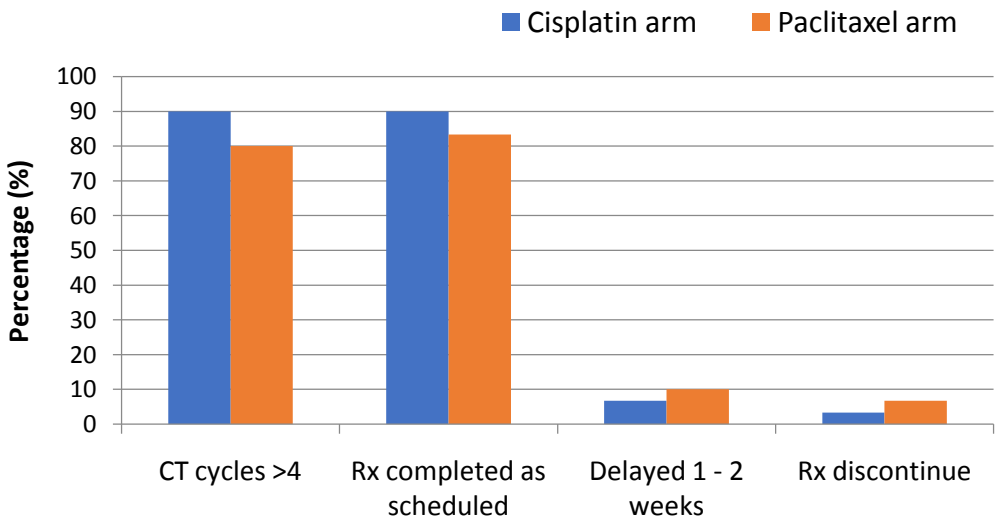

Figure II above shows, chemotherapy had to be discontinued in two patients of paclitaxel arm and one patient of cisplatin arm because of drug-related toxicities. Also, delay in chemotherapy was slightly common with paclitaxel arm than cisplatin arm (10.0 vs 6.7).

Table IV Response rates of the patients (N=30)

Table IV below shows response assessment was done 3 months after completion of treatment. Complete response was achieved 63.3% in cisplatin arm and 56.7% in paclitaxel arm. This difference was not statistically significant as the p-value was not significant.

	Cisplatin arm	Paclitaxel arm	p-value
Complete response	19 (63.3)	17 (56.7)	0.796^{ns}
Partial response	7 (23.3)	6 (20.0)	

Progressive disease	3 (10.0)	5 (16.7)
Discontinue R_x	1 (3.3)	2 (6.6)

Discussion:

The present study was a single institution, hospital based, prospective, randomized trial evaluating clinical response and toxicities of concurrent chemoradiation with weekly cisplatin versus weekly paclitaxel in the treatment of locally advanced cervical cancer (IIB-IVA). Results of this study demonstrated that concurrent chemoradiation with weekly paclitaxel was as effective as concurrent chemoradiation with weekly cisplatin.

In this study, Majority of the patients in both treatment arms were less than 50 years of age with no significant mean difference between two groups ($p>0.785$). In another study, among Hispanic women, rates of cervical cancer were found high specially in 40 years of age or older and in case of African-American women cervical cancer rate was high in more than 50 years of patients [10].

In case of parity, it has been observed that maximum number of patients in this study were multiparous (number of child birth >=2). Similar result is also found in previous study [11].

Regarding treatment toxicities, in the paclitaxel group, there were higher frequencies of grade I & II peripheral neuropathy.Similar toxicity has been reported by previous studies. One of the studies found grade I or grade II peripheral neuropathy [12].

Follow-up period was of 3 months for entire group. response assessment was done 3 months after completion of treatment. Complete response was achieved 63.3% in cisplatin arm and 56.7% in paclitaxel arm, again, partial response was 23.3% in cisplatin arm and 20% in paclitaxel arm. Similarly in other study, the complete response and partial response rates on paclitaxel monotherapy were significantly lower compared with the cisplatin regimens (42% v 67%)[13].

This is confirmed by results of many trials where paclitaxel protocols are as effective as the cisplatin in concurrent chemoradiation, regardless of disease stage. In the present study, patients treated with paclitaxel were safe and showed acceptable and manageable toxicity and locoregional control.

Conclusion:

Concurrent chemoradiation with weekly paclitaxel seems to be an alternative option in the treatment of locally advanced carcinoma of cervix in cisplatin contraindicated cases both in

terms of response and toxicity. But more multi-institutional studies are required with large number of patients and with longer follow up.

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