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Original Research Article

Prospective randomised study comparing concomitant chemoradiotherapy using weekly paclitaxel versus weekly cisplatin in locally advanced carcinoma cervix (FIGO STAGE IB2 – IVA) in a tertiary care hospital

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ABSTRACT

Background: Concomitant chemoradiation(CRT) with weekly Cisplatin is presently the treatment of choice for locally advanced cases of carcinoma cervix. Despite it's proven benefit in reducing disease recurrence by as much as 50%, our search is on for further improvement of treatment efficacy.
Aims: This trial was done for comparing the response and toxicity of CRT with weekly Paclitaxel versus weekly Cisplatin in carcinoma cervix with locally advanced staging.
Materials and Methods: Biopsy proven cases of squamous cell Ca stage IB2 to IVA were randomized into two arms (1:1 ratio). Arm A- patients received concomitant weekly cisplatin(40mg/m2)for 5 weeks during external radiation. For arm B-patients received weekly paclitaxel(60mg/m2) for 5 weeks concomitantly. EBRT dose of 50.4 Gy in 28 #was given alongwith followed by brachytherapy. Institutional and ethical clearance was obtained.
Conclusion: Paclitaxel, when given concurrently with EBRT in cases of carcinoma cervix with locally advanced staging produces comparable response to that of cisplatin.

1. Introduction

Cervical cancer ranks among the most prevalent cancers globally. In India, it accounts for about 6-29% of all cancers diagnosed in women.[1] The absence of widespread screening programs in India results in many cases being diagnosed at advanced stages,[2,3] making cervical cancer a leading cause of cancer-related deaths in the country.[4] Over 90% of these cases are squamous cell carcinomas, while adenocarcinomas make up approximately 7% to 10%. Currently, concurrent chemoradiation (CRT) with weekly Cisplatin is the preferred treatment for locally advanced cervical cancer. While this treatment has demonstrated a significant reduction in disease recurrence by up to 50%, efforts continue to enhance treatment outcomes by improving response rates and minimizing side effects. This study aims to compare the efficacy and side effects of CRT using weekly Paclitaxel versus weekly Cisplatin in treating locally advanced cervical cancer.

2. Materials and Methods

This was a prospective, longitudinal study conducted at a single institution. Patients eligible for inclusion underwent thorough history assessments, essential clinical evaluations, and gynecological examinations.

Inclusion criteria of our study was as follows-

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1. Biopsy proven cases of carcinoma of uterine cervix considered suitable for curative treatment with definitive radio-chemotherapy.
2. Histopathology type- squamous cell carcinoma or adenocarcinoma.
3. FIGO stage IB2- IVA (According to FIGO 2018).
4. Age 18-below 70 years.
5. ECOG Performance Status 0-2.
6. Normal baseline hematological and biochemical parameters.
7. Signed Informed consent to participate in the study.

Those fulfilling the inclusion criteria were randomly assigned to two groups using computer-generated randomization. In Arm A (the Cisplatin control group), patients received an external beam radiation therapy (EBRT) dosage of 50.4Gy administered over 28 fractions spanning 5.5 weeks, coupled with weekly cisplatin doses of 40mg/m^2 for the same duration, following appropriate pre-medications and adequate hydration during the radiation treatment. Conversely, patients in Arm B underwent identical EBRT dosing and fractionation but received concurrent weekly paclitaxel at a dosage of 60mg/m^2. After completing their respective treatments, patients underwent rigorous follow-ups at three-month intervals until the study's conclusion. These follow-ups included clinical examinations and relevant imaging studies to monitor for locoregional recurrence and distant metastases.

2.1. Radiotherapy

The Theratron 780-C Telecobalt machine was predominantly used in this study, as it is widely available in low and middle-income countries. All participants received treatment using this Telecobalt machine. Following the external beam radiation therapy (EBRT), a pelvic assessment was conducted to evaluate geometric considerations, disease response, and the potential for intracavitary brachytherapy (ICBT). Patients demonstrating favorable geometry and either complete or near-complete response underwent ICBT within a week after completing EBRT, once acute grade 3 and 4 adverse events had subsided. Conversely, those with unfavorable geometry, partial response, no response, or stable disease received interstitial brachytherapy.

To evaluate clinical response, assessments were conducted post-EBRT, post-brachytherapy, and subsequently at three-month intervals using CT/MRI imaging of the pelvis and RECIST criteria within three months post-treatment. Acute toxicity was monitored weekly throughout EBRT, after treatment completion, and at the initial follow-up, adhering to the CTCAE version 4.0 from the National Cancer Institute in Bethesda. Initial patient follow-ups included comprehensive physical and gynecological examinations, with subsequent evaluations at six months incorporating appropriate blood tests and imaging studies. The RTOG criteria for late morbidity were employed to evaluate long-term toxicities.

2.2. Statistical analysis

All patients meeting the study criteria were enrolled in this non-randomized trial. Data collection was systematically organized using a preformatted Microsoft Excel Worksheet from Office 2010 (Microsoft Inc., USA). Statistical analyses for categorical data were conducted using SPSS version 21 (SPSS Inc., USA). Data were presented as percentages and assessed using either Fisher's exact test or the Chi-square test. Continuous data were expressed as mean ± standard deviation (SD) and compared using an independent T-test. All statistical tests were two-tailed, considering a P-value of <0.05 as indicative of statistical significance. Survival analyses were conducted utilizing the Kaplan-Meier Survival Plot method.

3. Result

The study was conducted in the department of Radiotherapy, RGKAR medical college and hospital, Kolkata. 80 patients who satisfied the eligibility criteria were accrued in the study conducted from January 2019-January 2020 and then followed up till July 2021. 31 patients in the study group and 32 patients in the control group were analyzed.

In my present study, the median age of presentation was 50 years (range 32-62 years). Majority of the patients presented with FIGO stage IIB-41.9% followed by stage IIA 25.8% & stage IIIB-12.9%, 9.7% cases were in stage IVA whereas 6.5% were in stage IIIC1 and IB2,3.2% being in stage IB3 and IIIC2. Among them 54.8% were well differentiated, 35.5% were moderately differentiated and 9.7% were poorly differentiated squamous cell carcinoma. In the study arm, stage IIB accounted for 34.4% patients followed by IIIB 25% and IVA 12.5% and the rest 28.1% in stage IB, IIA & IIIC. 50% of patients had moderately differentiated squamous cell histology in the study arm. In the control arm, stage IIB accounted for 44.4% patients followed by IIA 26% and IVA 10.5% and the rest 19.1% in stage IB, IIIB & IIIC.

3.1. Concurrent chemotherapy

The median number of cycles of weekly taxanes was 5 against in cisplatin arm. Out of 63 patients 61.7% completed the scheduled treatment within 8 weeks of the start of treatment while 38.3% completed it beyond 8 weeks. (Table 1) All patients received 2 fractions of brachytherapy. Mean dose per fraction being 8.55 for Study arm B and 8.34 for arm A.(Table 2)

64.5% in study arm showed grade III anemia versus 84.4% in control arm, 74.2% showed grade III myelosuppression with Paclitaxel versus 75% with

Table 1: Treatment time parameters

Study arms		EBRT (Days)	Total Treatment Time (Days)
	Median	42.00	57.00
	Mean	42.90	58.81
Paclitaxel (Study arm B)	Std. Deviation	4.935	9.101
	Minimum	37	42
	Maximum	58	77
	Median	40.00	62.00
	Mean	43.25	62.44
Cisplatin (Study arm A)	Std. Deviation	6.653	8.171
	Minimum	37	48
	Maximum	65	79
	Median	41.00	59.00
	Mean	43.08	60.65
Total	Std. Deviation	5.826	8.764
	Minimum	37	42
	Maximum	65	79
	P value	0.815	0.101

Table 2: Brachytherapy dose (Gy) per fraction

Study arms	N	Median	Mean	S.D	Minimum	Maximum
Paclitaxel Study arm B)	31	9.00	8.55	0.568	7	9
Cisplatin (control arm A)	32	9.00	8.34	0.937	6	9
Total	63	9.00	8.44	0.778	6	9

p value 0 301. All patients received 2 fractions of brachytherapy

Table 3: Adverse events comparison between study arms - the acute toxicities were graded as per Common Terminology Criteria for Adverse Events (CTCAE) version 4

Adverse events		Study arms: Paclitaxel Count	Paclitaxel Column N %	Cisplatin Count	Cisplatin Column N %	P value
Haemoglobin level decrease _ALL_Grades	No	9	29.0%	5	15.6%	0.201
	Yes	22	71.0%	27	84.4%	
Haemoglobin level decrease _Grade 3	No	20	64.5%	27	84.4%	0.070
	Yes	11	35.5%	5	15.6%	
Absolute Neutrophil Count decrease _All_Grades	No	8	25.8%	6	18.8%	0.501
	Yes	23	74.2%	26	81.2%	
Absolute Neutrophil Count decrease _Grade 3	No	23	74.2%	24	75.0%	0.941
	Yes	8	25.8%	8	25.0%	
Neuropathy_all Grades	No	9	29.0%	31	96.9%	0.000
	Yes	22	71.0%	1	3.1%	
Neuropathy_Grade 3	No	28	90.3%	31	96.9%	0.286
	Yes	3	9.7%	1	3.1%	
Nausea_all_Grades	No	7	22.6%	5	15.6%	0.482
	Yes	24	77.4%	27	84.4%	
Nausea_Grade 3	No	25	80.6%	27	84.4%	0.697
	Yes	6	19.4%	5	15.6%	
Ototoxicity_ALL Grades	No	31	100.0%	16	50.0%	0.000
	Yes	0	0.0%	16	50.0%	

Cisplatin, grade III neuropathy were found in 9.7% in Study arm only 3.1% in Control arm, percentage showing nausea was almost equal in both arms (80.6% vs 84.4%-all grades).Nearly 50% showed ototoxicity alone in Cisplatin arm. (Table 3) Nephrotoxicity was more in Cisplatin arm-12.5% were in grade III while it's only 3.2% in Paclitaxel arm as the follow up period was shorter relatively little late toxicity could be noted. Late rectal toxicities were slightly higher in paclitaxel arm. Significant late bladder toxicity/grade III toxicities could not be seen in either arm till last phase of follow up. However, constitutional toxicities were found to be on the higher side in control arm even after 6-8 months of treatment completion.

3.2. Response assessment

During evaluation of response to the treatment protocol, patients in the two arms were marked as complete responders(CR),partial responders(PR) and non responders. 96.8% of patients had Partial Response after EBRT in Study arm versus 87.5% in Control arm with only one patient showed Complete Response in Paclitaxel arm and four in Cisplatin arm- respectively post EBRT (p value 0.173). Following brachytherapy Complete Response rate rose to 93.5% in Paclitaxel arm versus 93.8% in Cisplatin arm, p value being 0.974. Median duration of follow up was 24 months (calculated by Reverse Kaplan Meier Survival analysis). Progression Free Survival in months was calculated as time form biopsy till disease progression. 7 patients in paclitaxel arm against 8 patients in cisplatin arm had disease progression, log rank test 0.126. Median PFS was not reached at the time of writing this article (Table 4 and Figure 1)

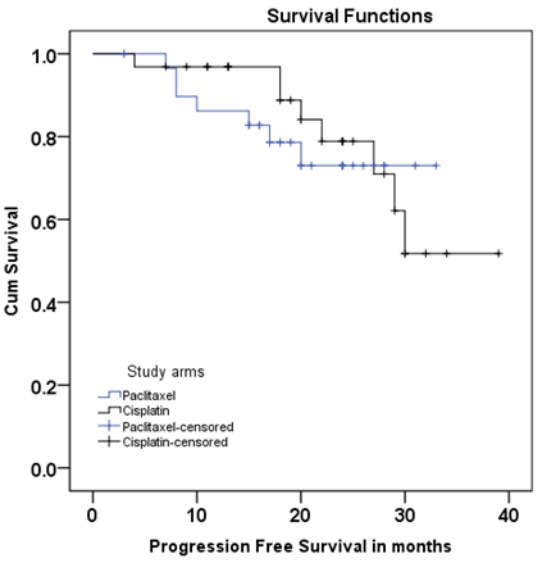

Figure 1: Kaplan Maier Survival analysis plot comparing PFS of Both the arms

4. Discussion

The role of concurrent paclitaxel in treating cervical cancer remains relatively understudied. This trial aimed to compare the efficacy and side effects of weekly paclitaxel versus weekly cisplatin in treating locally advanced cervical cancer.

Participants included those diagnosed with FIGO stages IB2 to IVA cervical cancer. Unlike Western countries where cervical cancer incidence peaks between the fifth and sixth decades, in India, it's most prevalent between ages 50-54, aligning with the average age of 50 observed in this study. The illiteracy rate was 45.2% in the study group and 34% in the control group.

While external beam radiation therapy (EBRT) was previously the primary treatment for locally advanced cervical cancer, its efficacy was limited. The introduction of concurrent cisplatin, based on RTOG 90-01 results, showed promise. However, alternative treatments with improved efficacy and safety are continually sought. Although drugs like hydroxyurea, 5-fluorouracil, and gemcitabine were explored, none surpassed cisplatin's effectiveness.[5–8]

Paclitaxel was initially used for metastatic and recurrent cervical cancer cases. Limited research exists on paclitaxel, either alone or combined with cisplatin in concurrent chemoradiation.[9–12] For instance, a study by Thakur et al. in 2011-2012 compared standard cisplatin (40 mg/m^2 weekly for 5 weeks) against a combination of cisplatin (30 mg/m^2) and paclitaxel (50 mg/m^2) weekly for 5 weeks. While both groups showed high response rates, adverse events were more frequent in the combination group.[13]

Another Korean study explored paclitaxel and carboplatin's efficacy in patients post-radical hysterectomy. The majority completed treatment with manageable side effects, leading to favorable survival rates.[14]

Regarding patient compliance, weekly cisplatin adherence varies between 50%-90%. In contrast, a phase II trial reported 80% compliance with weekly paclitaxel.[15] Interestingly, our study found better compliance with cisplatin (83%) than paclitaxel (60%), possibly due to higher cisplatin dosages. Side effects differed between the groups, with cisplatin primarily causing gastrointestinal issues and paclitaxel leading to fatigue and hematological issues.

Post-EBRT, patient responses were comparable between the groups. However, with brachytherapy, response rates were similar, with slight variations in disease progression. Limitations of our study included a small sample size and relatively short follow-up duration. To fully assess long-term outcomes and toxicity, larger studies with extended follow-up periods are essential.

Table 4: Mean PFS in months with Kaplan Maier Survival analysis plot. Median PFS was not reached.

Study arms	Mean PFS			
Estimate Std. Error	95% Confidence Interval			
		Lower Bound	Upper Bound	
Paclitaxel	27.573	1.798	24.049	31.098
Cisplatin	31.664	2.040	27.666	35.661
Overall	31.084	1.685	27.780	34.387

5. Conclusion

Paclitaxel based concurrent chemoradiation might be an alternative to standard cisplatin based chemoradiation in management of locally advanced cervical cancer, with acceptable toxicities. Further multi-institutional studies are required to evaluate the actual efficacy of paclitaxel, especially in individuals with renal compromise.

6. Source of Funding

None.

7. Conflict of Interest

None.

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