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Exploring Enhanced Efficacy: A Comparative Analysis of Weekly Paclitaxel and Cisplatin in Concurrent Chemoradiotherapy for Locally Advanced Cervical Carcinoma

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Abstract

Objective: This prospective comparative study aimed to assess the efficacy and safety of weekly paclitaxel in concurrent chemoradiotherapy (CCRT) compared to the standard of care, weekly cisplatin, for locally advanced cervical carcinoma (LACC) in stages IB2-IIIC1. The primary objective was to explore whether paclitaxel offers improved local control and post-therapy response rates compared to cisplatin, potentially leading to better survival outcomes.

Methods: The study, conducted at RNT Medical College, Udaipur, enrolled sixty-two eligible patients with stage IB2-IIIC1 cervical carcinoma. Patients were randomly assigned to two arms: Arm A (cisplatin) and Arm B (paclitaxel). Both arms received radiotherapy, and paclitaxel or cisplatin was administered intravenously weekly. Monitoring included weekly assessments for toxicities during treatment and monthly evaluations for three months post-treatment. Response and toxicities were evaluated through imaging and clinical examinations.

Results: Demographic analysis revealed comparable characteristics between the two arms. Notably, the study identified differences in acute toxicities, with the paclitaxel arm exhibiting lower renal toxicity but higher neurological reactions. Acute gastro-intestinal toxicity, particularly nausea and vomiting, was more pronounced in the cisplatin arm. Hematological toxicities, such as neutropenia and anemia, varied between the arms.

Conclusion: The study concluded that concurrent weekly paclitaxel with radiation therapy in LACC provides a response comparable to standard concurrent cisplatin with radiation therapy. While paclitaxel demonstrated manageable toxicities, including increased neurological reactions and anaemia, cisplatin exhibited a slightly better response with a higher incidence of nausea and vomiting. The findings suggest that concurrent weekly paclitaxel can be considered as an alternative to weekly cisplatin, especially in patients with a higher susceptibility to nausea and vomiting.

Keywords: Locally advanced cervical carcinoma, concurrent chemoradiotherapy, cisplatin, paclitaxel, efficacy, toxicity, response rates, survival outcomes

Introduction

Cervical cancer accounts for 18.3% of all female cancer cases, making it the second most common disease among Indian women. GLOBOCAN 2020 states that there is an annual incidence of 1,23,907 and a 5-year prevalence of 2,25,689 among Indian women. The fact that cervical cancer is responsible for 77,348 yearly fatalities highlights how serious the problem is. Patients in stages IB2-IIIC1, where the

prognosis is particularly bad, are disproportionately affected. For locally advanced cervical cancer (LACC), aggressive radiation treatment has been the main therapeutic strategy for the past century.[1] Significant progress was made between 1999 and 2002, when two large meta-analyses and four important randomized studies reported improved survival rates with cisplatin-based concurrent chemoradiotherapy (CCRT). As a result, weekly injection of 35–40 mg/m^2 of cisplatin, in addition to regular radiation treatment, has been defined as the "standard of care" for International Federation of Gynecology and Obstetrics (FIGO) stage IB2-IIIC1 cervical cancer.[2]

Even with these advances, many patients still fail to respond to treatment; the main causes of treatment failure are locoregional recurrence or chronic pelvic illness. Large, bulky original tumors with hypoxic zones and the existence of malignant clones resistant to chemotherapy and/or radiation treatment are among the reasons that contributed to this failure. As a result, research into other concurrent combinations that could provide better clinical effectiveness is becoming more and more popular.[3]

Although weekly cisplatin combined with CCRT has emerged as the "standard of care" for LACC therapy, studies investigating different chemotherapeutic agents in the contemporaneous setting continue with the goal of improving response rates and local control. Renowned for its effectiveness in treating solid tumors, paclitaxel has shown encouraging outcomes when used as a neo-adjuvant treatment in lung, breast, and ovarian malignancies as well as in recurrent or metastatic cases. It's a good fit for radiation treatment integration because of its selective cytotoxic effect in cervical cancer cells with minimal Raf-1 kinase activity.[4] A maximum tolerated dose (MTD) of 50 mg/m^2 per week in conjunction with radiation has been established by phase I studies, which have validated the clinical feasibility of CCRT with paclitaxel. Paclitaxel's therapeutic effectiveness in treating metastatic and recurrent cervical cancer has also been investigated in phase II and III studies, which have shown objective response rates ranging from 36% to 47%.[5]

The purpose of this prospective trial is to evaluate the efficacy and safety of weekly paclitaxel combined with CCRT with the accepted practice of weekly cisplatin for cervical cancer in stages IB2-IIIC1. This study is based on the hypothesis that greater local control and a higher post-therapy response rate will eventually result in a benefit to survival.[6]

Materials And Methods

Study Setting: This prospective comparative study was conducted at RNT Medical College, Udaipur (Rajasthan), and involved a cohort of a minimum of sixty-two eligible patients diagnosed with stage IB2-IIIC1 cervical carcinoma, satisfying predefined eligibility criteria.

Inclusion Criteria:

1. Histopathologically confirmed cervical carcinoma.
2. Advanced stage (FIGO stage IB2 to IIIC1).
3. Biopsy-proven squamous cell carcinoma.
4. Age between 18 and 70 years.
5. Normal hematological and biochemical parameters.
6. ECOG performance score 1 & 2.
7. Willingness to provide written informed consent.

Exclusion Criteria:

1. Recurrent disease.
2. Prior pelvic radiotherapy or chemotherapy.
3. Presence of synchronous double primary malignancies.
4. Pregnancy.
5. Simultaneous participation in another clinical study.
6. Enlarged para-aortic lymph nodes.

Pre-treatment Evaluations:

1. Comprehensive medical history, including marital status, number of children, and lifestyle factors.
2. Thorough physical examination, including pelvic examination.
3. Complete hematological and biochemical profile assessment.

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4. Chest X-ray P-A view, USG whole abdomen, contrast MRI abdomen-pelvis, and, if necessary, sigmoidoscopy or cystoscopy.
5. Histopathological study.

Randomization and Treatment Arms: Following pre-treatment evaluation, patients were randomly assigned to two arms: Arm A (n=31) receiving 35-40 mg/m^2 cisplatin weekly and Arm B (n=31) receiving 50 mg/m^2 paclitaxel weekly. Both arms underwent radiotherapy (44-50 Gy, 2 Gy per fraction) using a telecobalt machine. Paclitaxel (50mg/m^2) or cisplatin (35-40mg/m^2) was administered intravenously one to two hours before each weekly radiotherapy session. Intracavitary brachytherapy was performed with a one-week gap after external beam radiotherapy (EBRT) completion, involving three sessions (7 Gy each, 1 week apart).

Monitoring and Evaluation: Patients were closely monitored for toxicities weekly during treatment and monthly for three months post-treatment. Toxicities were assessed using Radiation Therapy Oncology Group Acute Radiation Morbidity Criteria (RTOG) for radiotherapy and Common Terminology Criteria for Adverse Events (CTCAE) for chemotherapy. After three months, treatment response was evaluated using contrast MRI of the pelvis, comparing findings with pretreatment MRI, and confirmed by loco-regional examination.

Patient Flow:

1. Histopathologically proven FIGO stage IB2 to IIIC1 cervical cancer.
2. Eligible patients providing informed consent.
3. Pre-treatment evaluation.
4. Randomization into Arm A (n=31, cisplatin) and Arm B (n=31, paclitaxel).
5. Weekly treatment sessions: Cisplatin 35-40 mg/m^2 or Paclitaxel 50 mg/m^2 concurrent with radiotherapy.
6. External beam radiotherapy (44-50 Gy).
7. Intracavitary brachytherapy (three sessions, 7 Gy each, 1 week apart).
8. Close monitoring for toxicities and response evaluation for three months.
9. Exclusion of one patient from each arm due to poor compliance.
10. Assessment of response and toxicities.

Results

Table 1:Demographic Differenciation

SN	Characteristics	Arm-A (n=31)	Arm-B (n=31)
1.	Age (in years)		
	Median	50	48
	Range	30-67	25-70
2.	Parity(no. of children)		
	≤3	21	19
	>3	10	12
3.	Stage		
	IIA	07	10
	IIB	13	12
	IIIA	03	00
	IIIB	08	06

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	IIIC1	00	03
4.	Histology		
	Well-differentiated SCC	10	09
	Moderately-differentiated SCC	15	17
	Poorly-differentiated SCC	06	05
5.	Performance Status (ECOG)		
	0	00	00
	1	12	11
	2	19	20
6	Receiving 5 cycle CCRT	05	06
7	Receiving 4 cycle CCRT	25	24

Acute Toxicities - All the acute toxicities of the two arms were summarized separately.

Table 2: Electrolyte Imbalance

Toxicity	Arm-A (n=30)	Arm-B (n=30)	p-value	Significance at p<0.05
Hyponatremia	3 (10%)	1 (3.34%)	0.31	Not significant
No Hyponatremia	27	29		
Hypokalemia	1 (3.34%)	0	0.28	Not significant
No Hypokalemia	29	30		

Electrolyte imbalance in form of hyponatremia was occurred in 10% patients of arm-A and 3.34% patients of arm-B without any statistically significant difference.

Electrolyte imbalance in form of hypokalemia was occurred in 3.34% patients of arm-A and 00% patients of arm-B but with no statistically significant difference.

Those patients who suffered from hyponatremia were managed by hospitalization and 3% normal saline infusion.

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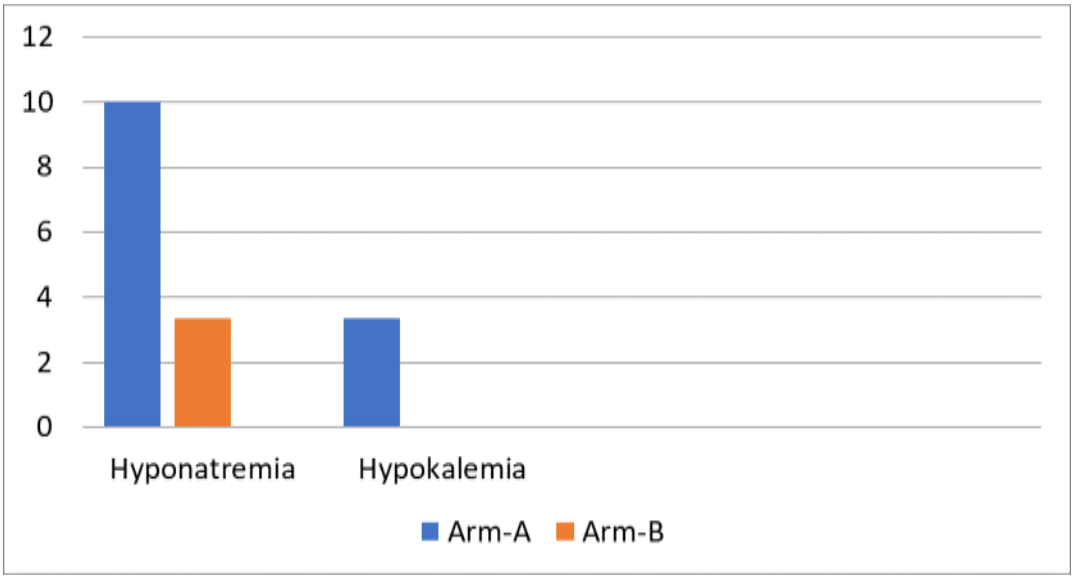

Table 3: Acute Gastro-Intestinal Toxicity

Acute gastro-intestinal toxicity		Arm-A (n=30)	Arm-B (n=30)	p-value	Significance at p<0.05
Nausea		21(70%)	10(33.33%)	**0.004**	Significant
No Nausea		9	20		
Vomiting (Grade)	I	09(30%)	05(16.67%)	**0.001**	Significant
	II	06(20%)	01(3.33%)		
	III	03(10%)	00		
	IV	0	00		
No Vomiting		12	24		
Diarrhoea (Grade)	I	03(10%)	05(16.67%)	0.11	Not significant
	II	01(3.33%)	04(13.33%)		
	III	00	00		
No Diarrhoea		26	21		

Acute gastro-intestinal toxicity in form of nausea (70%% v/s 33.33%) were occurred more in arm-B and this was statistically significant (p value=0.004).

Acute gastro-intestinal toxicity in form of vomiting showed statistically significant difference between both arms with **p value=0.001** [grade I (arm-A 30% v/s arm-B 16.67%), grade II (arm-A 20% v/s arm-B 3.33%), grade III (arm-A 10% v/s arm-B 0%) and there was no grade IV vomiting in any arm].

Acute gastro-intestinal toxicity in form of diarrhoea grade I (10% v/s 16.67%), grade II (3.33% v/s 13.33%) and there was no grade III diarrhoea in any arm.

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Table 4- Neurological Reaction

Toxicity	Arm-A	Arm-B	p-value	Significance at p<0.05
Neurological Reaction	02 (6.67%)	08 (26.67%)	**0.003**	Significant
No Neurological Reaction	28	22		

Neurological reaction occurred more in arm-B (26.67%) as compared to arm-A (6.67%) which is statistically significant (p value=0.03).

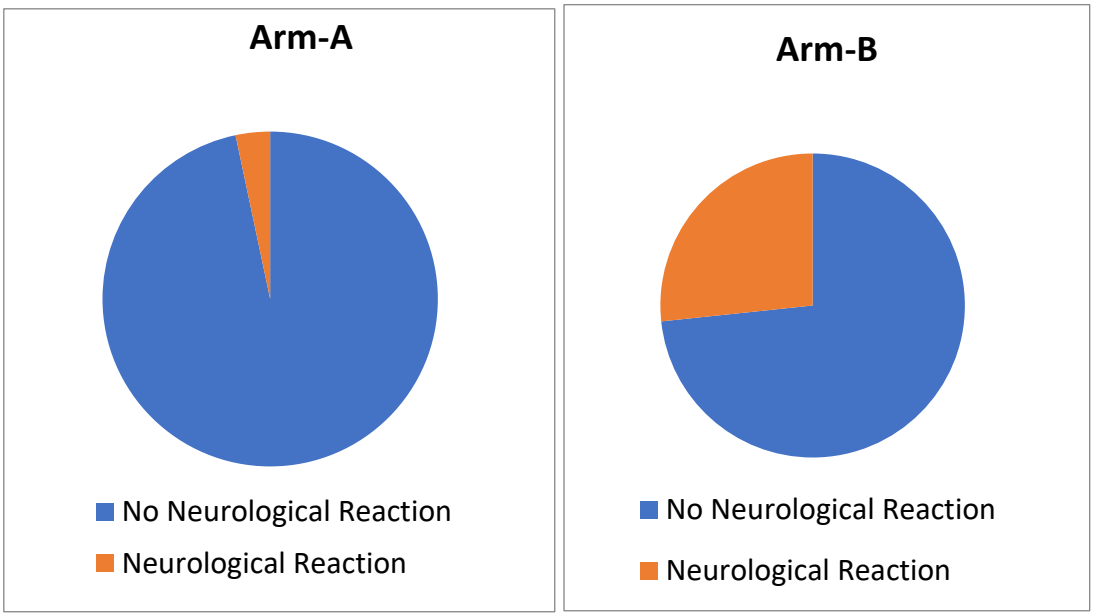

Table 5:Three Months After Treatment Completion

Response	Arm-A (n=30)	Arm-B (n=30)	p-value	Significance at p<0.05
CR	24 (80%)	21 (70%)	0.37	Not significant
PR	5 (16.67%)	7 (23.33%)	0.51	Not significant
SD	1 (3.33%)	2 (6.67%)	0.55	Not significant

CR:-Complete Response, PR:-Partial Response, SD:-Stable Disease

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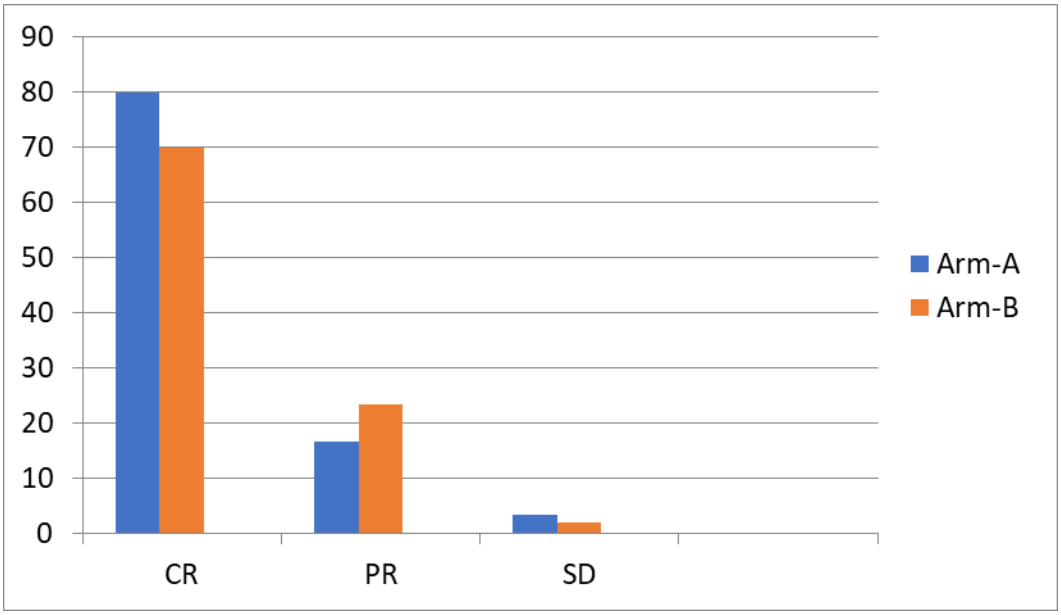

Discussion

The study, conducted on 62 newly diagnosed cervical cancer cases, aimed to compare acute toxicities and response rates between weekly cisplatin and weekly paclitaxel concurrent chemo-radiotherapy regimens. Despite the dropout of one patient from each arm due to poor compliance, the study provides valuable insights into the efficacy and toxicities associated with the two treatment approaches.[7]

The significance of concurrent chemo-radiotherapy, particularly with cisplatin, is well-established as the standard treatment for locally advanced cervical cancer. RTOG 90-01 results emphasize its role in reducing disease recurrence and death risk by 30%-50%.[7] However, ongoing efforts aim to identify alternative drugs with high activity to further improve survival and minimize recurrence risk. GOG 120, comparing weekly cisplatin with a three-drug regimen, found similar survival rates but increased toxicity with the addition of hydroxyurea. Khalil et al. explored the combination of weekly cisplatin and paclitaxel, highlighting its efficacy in providing good local control with a distinct toxicity profile.[8]

Tumor response at the 3-month follow-up was 100% in both arms, aligning with Japanese phase I study results using weekly cisplatin and paclitaxel. No significant advantage in response rate was observed for paclitaxel over cisplatin after 6 months. Regarding acute toxicities, the weekly cisplatin arm showed a higher incidence of acute renal toxicity compared to the paclitaxel arm, consistent with findings in similar studies. Electrolyte imbalances, specifically hyponatremia and hypokalemia, were more prominent in the cisplatin arm.[9]

In terms of hematological toxicities, both arms demonstrated no grade-IV or grade-I anaemia. Grade-II anaemia occurred equally in both arms, while grade-III anaemia was higher in the paclitaxel arm. Neutropenia was more pronounced in the weekly cisplatin arm, with higher grade-I and grade-II toxicities compared to paclitaxel. Notably, the study by Fady B et al. corroborated these findings, emphasizing the statistical significance of neutropenia differences.[10,11]

Acute gastro-intestinal toxicity, particularly nausea, occurred more in the weekly cisplatin arm. Vomiting and diarrhea, both of lower grades, also exhibited differences between the two arms, with Pabitra D et al. reporting similar trends. Skin toxicity, predominantly of lower grades, was observed in both arms, with no significant difference. Neurological reactions were more prevalent in the paclitaxel arm, a finding consistent with other studies.[12]

Conclusion

Based on the findings of the present study we concluded that concurrent weekly paclitaxel with radiation therapy in LACC produces comparable response to standard concurrent cisplatin with radiation therapy, but there was minor increased incidence of manageable acute toxicities like neurological reactions and anaemia. However, the concurrent weekly cisplatin with radiation therapy

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having slightly better response with higher incidence of nausea and vomiting. Thus, use concurrent weekly paclitaxel with radiation therapy is an alternative to weekly cisplatin, especially in patients having higher chances of nausea and vomiting.

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