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A PROSPECTIVE INTERVENTIONAL STUDY COMPARING WEEKLY CISPLATIN WITH WEEKLY CISPLATIN AND PACLITAXEL IN CHEMORADIATION OF CARCINOMA CERVIX

Radiotherapy

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ABSTRACT

Background: Cervical cancer remains a major health burden in developing countries. Cisplatin-based chemoradiation is the standard of care for locally advanced cervical cancer. However, recurrence and treatment failure remain significant. Paclitaxel, a radiosensitizer, has shown promise when combined with cisplatin. To compare the clinical outcomes and treatment-related toxicities of weekly cisplatin alone versus weekly cisplatin with paclitaxel during concurrent chemoradiation in carcinoma cervix. **Materials And Methods:** This prospective randomized interventional study included 90 patients with histologically confirmed carcinoma cervix (FIGO stage IIA2–IIIC). Patients were randomized into two groups: Arm A (cisplatin 30mg/m2 + paclitaxel 40mg/m2) and Arm B (cisplatin alone 30mg/m2). Both groups received IMRT (50gy in 25 fractions) followed by HDR brachytherapy (21gy in 3fractions). Acute toxicities were assessed weekly; response was evaluated at completion of treatment and at 3 and 6 months using RECIST criteria. **Results:** Complete response rates at 6 months were 95% in the cisplatin + paclitaxel group and 93% in the cisplatin group ($p = 0.5$). The cisplatin + paclitaxel arm had significantly higher rates of Grade II diarrhoea, nausea and vomiting, and proctitis ($p < 0.05$). Hematologic and nephrotoxic profiles were comparable. **Conclusion:** Adding paclitaxel to weekly cisplatin during chemoradiation for carcinoma cervix improves complete response rates numerically but increases acute toxicity significantly. Further studies are warranted to balance efficacy and tolerability.

KEYWORDS

INTRODUCTION:

Cervical cancer is the 4th most diagnosed cancer (6.9%) among women accounting for 662,301 cases and causing 348,874 deaths worldwide as per GLOBOCAN 2022.

In India, cervical cancer is the 3rd most diagnosed cancer (9.0%) overall and the 3rd most common cause of cancer mortality (8.7%). It is the 2nd most common among women (17.7%) in incidence as well as mortality accounting for almost 127,526 of all newly diagnosed cancer cases in women after breast cancer and causing 79,906 Cancer related deaths with the 5-year prevalence being 339,589 cases[1] .

Carcinoma cervix is a common malignancy in developing countries especially in rural areas. More than 90% of cervical cancer are related to presence of human papilloma virus (HPV) infection and are contracted via sexual intercourse [2]. Specific types of oncogenic HPV strains are 16, 18 and other less frequent subtypes are 6, 11, 31, 33, 35, 39, 45, 51, 52, 56 and 58 have been well characterized as causative agents for cervical cancer, with some geographic variation[3]. HPV is the central cause of almost all cervical cancers and its precursor, cervical intra epithelial neoplasia (CIN). A proportion of CIN, if not detected and treated, progresses to invasive cervical carcinoma over a period of 10-20 years owing to the effect of other cofactors.

Definitive treatment in locally advanced cancer cervix is chemoradiotherapy followed by brachytherapy. External beam radiation therapy is used to treat the central disease and to sterilize known or suspected regional metastases. For patients with bulky central disease, a course of EBRT to the pelvis usually causes significant tumour regression, potentially improving the dose distribution of subsequent intracavitary radiation by shrinking the bulky endocervical disease or by reducing exophytic tumour. It is recommended to keep the total treatment duration of 49 days and not more than 56 days.

The American Brachytherapy Society recommends use of multiple intracavitary brachytherapy insertions to allow progressive tumour volume reduction, allowing more effective disease coverage with the subsequent application. External beam irradiation is given at a total dose of 45Gy (40-50Gy) in five weeks. When external beam irradiation and high dose rate (HDR) intracavitary brachytherapy are combined, the goals are to treat point A to a low dose rate (LDR) equivalent of 80 Gy for small volume cervical tumor and >85 Gy for large volume tumor[4]. Gross disease in the parametria treated with tightly contoured external beam boosts to 60-65 Gy. Every attempt is made to keep the bladder dose below low dose rate equivalent to 80 Gy and the rectal dose is below 75Gy.

The findings from five randomized clinical trials (GOG-85, RTOG-9001, GOG-120, GOG- 123, and SWOG-879) have demonstrated superior outcomes in overall survival (OS), progression-free survival (PFS), and locoregional disease control in patients with cervical cancer who underwent cisplatin-based chemoradiation therapy[5-8] .Chemotherapy, when administered concurrently with radiation, serves to eliminate micrometastases and enhance the radiosensitivity of tumour cells. Accordingly, chemotherapeutic agents used in this context must possess both antineoplastic activity against cervical carcinoma and radiosensitizing properties.

However, despite the incorporation of cisplatin in concurrent chemoradiotherapy, a considerable proportion of patients continue to experience both locoregional and distant recurrences[9]. A Cochrane Database systematic review assessing concurrent chemoradiation in cervical carcinoma reported an absolute gain of approximately 10% in overall survival and 13% in progression-free survival, independent of whether platinum-based agents were utilized[10].

Numerous cytotoxic agents—including carboplatin, paclitaxel, 5-fluorouracil, and gemcitabine—have been investigated in this setting. Although these agents have shown some efficacy in cervical cancer, particularly in recurrent or metastatic disease, enhancements in overall survival and tolerability remain modest. Therefore, continued exploration of alternative therapeutic regimens is warranted.

The combination of cisplatin and paclitaxel has been evaluated in recurrent and metastatic cervical cancer and has demonstrated both safety and efficacy. The Gynecologic Oncology Group (GOG) observed a 17% response rate with single-agent paclitaxel in advanced squamous cell carcinoma of the cervix[11]. Moreover, the cisplatin-paclitaxel combination has been investigated in various Phase II and III studies in metastatic or recurrent disease, with objective response rates ranging from 36% to 46%[12-14].

The present study aims to compare standard cisplatin-based chemoradiotherapy with a cisplatin-paclitaxel combination regimen in terms of treatment-related toxicity profiles and tumor response in

patients with carcinoma of the uterine cervix.

MATERIALS AND METHODS:

This is a prospective, comparative study in patients with histologically proven squamous cell carcinoma presenting in radiation oncology department. The cases were randomly distributed among the two groups. Randomization was done based on the chit box method with replacement.

Patients eligible for the study included those with histopathologically confirmed squamous cell carcinoma of the cervix, aged between 20 to 70 years. Eligible participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and disease staged as FIGO IIA2 to IIIC. Additional inclusion parameters included normal hematological, renal, and hepatic function, and provision of informed written consent.

Patients were excluded from the study if they had a prior history of treatment for cervical carcinoma, including surgery, chemotherapy, or radiotherapy. Other exclusion criteria included the presence of double malignancy, pregnancy or lactation, and any significant comorbid condition such as uncontrolled hypertension, diabetes mellitus, or immunocompromised status.

Plan Of Action

90 cervical cancer patients fulfilling the inclusion criteria were selected. Patients were randomly assigned to the study and control arms using the chit box method with replacement.

ARM A (Study Arm) : 45 Patients were treated with concurrent weekly cisplatin (30mg/m2) and paclitaxel (40mg/m2) along with intensity modulated radiation therapy (IMRT) followed by brachytherapy.

ARM B (Control Arm): 45 Patients of this arm were treated with weekly cisplatin (30mg/m2) along with intensity modulated radiation therapy (IMRT) followed by brachytherapy.

Radiation Technique

All patients were treated with IMRT by linear accelerator in supine position after proper immobilization. The area to be scanned was localized and required axial scans of 3mm slices were obtained. For EBRT planning and treatment, CT scans were taken and used for target delineation. GTV, CTV, PTV & OAR marked according to RTOG guidelines. A total dose of 50 Gy in 25 fractions with 200 CGY/# was given over five weeks.

Brachytherapy

Brachytherapy was delivered one week after completion of EBRT with HDR technique using cobalt-60 source at the dose of 700 CGY in 3 fractions weekly.

Toxicity Assessment

Weekly clinical examinations, haematological, and clinical parameters were used for the assessment of acute toxicities using CTCAE 5.0 (National cancer institute, common terminology criteria for adverse event scale).

Treatment Response

Evaluation was conducted after the completion of the treatment, and the patient was followed up at 3 and 6 months. Patients were evaluated through history, clinical examination, and CECT pelvis/CEMRI pelvis. The RECIST (Response Evaluation Criteria in Solid Tumour) was utilized for response evaluation.

All patients were followed up for at least 6 months. During each scheduled follow-up, a mandatory gynaecological examination was performed.

Statistical Analysis:

Mean values between the two arms were compared for the test of significance using the unpaired t test. Inter arm mean differences were compared for the test of significance using paired t test. For comparing proportions of different events between the two arms. p value less than 0.05 has been considered significant. All data was analysed using SPSS version 26.

RESULTS

A total of 84 patients complete the treatment with histologically confirmed squamous cell carcinoma of the cervix were enrolled and randomly assigned to two treatment arms:

Study Arm (n = 42): Received weekly cisplatin (30 mg/m²) + paclitaxel (40 mg/m²) with concurrent radiotherapy.

Control Arm (n = 42): Received weekly cisplatin (30 mg/m²) with concurrent radiotherapy.Baseline demographic and clinical characteristics were well matched between the two arms. The mean age was 51.57 years in the study arm and 50.78 years in the control arm ($p = 0.734$). Most patients belonged to the 41–60 age group and came from lower or middle socioeconomic strata.

No significant differences were noted in terms of ECOG performance status ($p=0.581$) or FIGO staging ($p=0.966$). However, histopathological subtype distribution differed significantly between groups ($p = 0.015$), with the study group having a higher proportion of poorly differentiated squamous cell carcinoma.

Tumor Response

At Completion of Intracavitary Brachytherapy (ICBT)

Complete Response (CR) 88% in the study arm vs 74% in the control arm ($p = 0.06$), Partial Response (PR): 12% vs. 24% (study vs. control) and Stable Disease (SD): 0% vs. 2% (study vs. control)

At 3 Months Post-Treatment

CR: 93% (study) vs. 85% (control), $p = 0.5$, PR: 7% (study) vs. 10% (control) and SD: 0% (study) v s. 5% (control)

At 6 Months Post-Treatment

CR: 95% (study) vs. 93% (control), $p = 0.5$, Progressive Disease: 5% (study) vs. 7% (control)

Although the study arm consistently showed higher complete response rates, none of the differences reached statistical significance.

Toxicity Profile

Toxicities were evaluated weekly during treatment using CTCAE v5.0. Grade II and above toxicities were more common in the study arm, particularly gastrointestinal side effects.

Gastrointestinal Toxicities

Diarrhoea: Significantly higher Grade II diarrhoea in the study arm from weeks 1 to 5 ($p < 0.05$ for each week). Week 5 Grade II: 26% (study) vs. 5% (control), $p = 0.01$

Nausea And Vomiting: Study group had significantly higher Grade II events throughout treatment ($p < 0.05$). Week 5 Grade II: 26% (study) vs. 5% (control)

Proctitis: Grade I proctitis was significantly more frequent in the study arm during multiple weeks ($p = 0.04$).

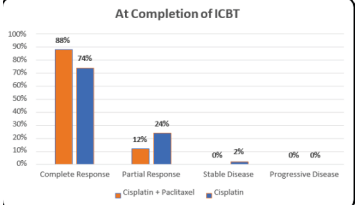
Haematological Toxicities

Anaemia, Neutropenia, Thrombocytopenia: Mild to moderate toxicities (Grade II) were more frequent in the study arm but did not reach statistical significance. Grade III anaemia and neutropenia were seen in 5% of the study arm and 2% of the control arm ($p > 0.05$).

Other Toxicities

Skin Toxicity: Grade II skin toxicity was higher in the study group but not statistically significant. Cystitis: Grade I cystitis showed a trend toward higher frequency in the study group without statistical significance. Nephrotoxicity: Similar profiles were observed in both arms, with no significant difference ($p > 0.05$).

Parameter	Cisplatin + Paclitaxel	Cisplatin	p-value
CR at ICBT Completion	88%	74%	0.06
CR at 3 Months	93%	85%	0.5
CR at 6 Months	95%	93%	0.5



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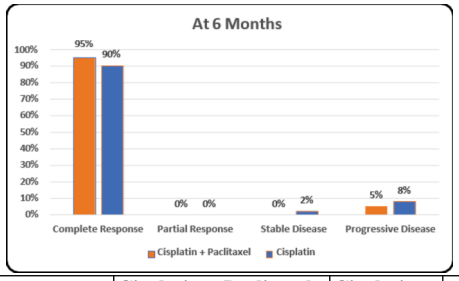
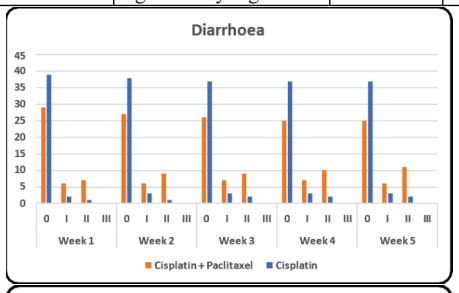
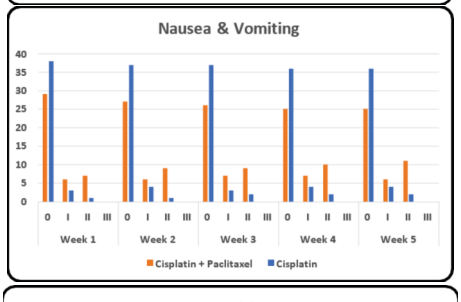
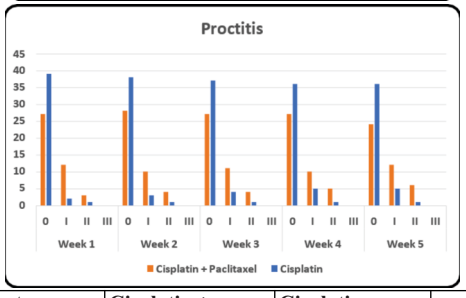


Parameter	Cisplatin + Paclitaxel	Cisplatin	p-value
Grade II Diarrhoea (Week 5)	26%	5%	0.01
Grade II Nausea & Vomiting	26%	5%	<0.05
Grade I Proctitis	Significantly higher	Lower	<0.05







Parameter	Cisplatin + Paclitaxel	Cisplatin	p-value
Grade III Anemia & Neutropenia	5%	2%	>0.05
Grade II Skin Toxicity	Higher (not significant)	Lower	>0.05

DISCUSSION

Overall, the paclitaxel + cisplatin group demonstrated a higher incidence of grade II toxicities, particularly for gastrointestinal toxicities like diarrhoea nausea and vomiting and grade I proctitis, indicating a greater toxicity profile compared to cisplatin group and it was statistically significant.

Other toxicities like anaemia, neutropenia, cystitis, skin toxicity and acute nephrotoxicity also showed trends towards Higher severity in cisplatin + paclitaxel group that when cisplatin was given alone this difference were not statistically significant.

Treatment response at the completion of Intracavitary brachytherapy and at 3 month and 6 month follow ups. At the completion of Intracavitary brachytherapy, the complete response rate was numerically higher in cisplatin plus paclitaxel group (88%) compared to the cisplatin group (74%). But this difference was not statistically significant.

At 3rd and 6th months, the complete response rates improved in both groups, but the study arm has consistently better complete response rate than control arm.

Concurrent chemoradiation using paclitaxel has been evaluated in different studies. Thakur et al.[15] comparing cisplatin based chemoradiotherapy and paclitaxel based chemoradiation. 81 new women with newly diagnosed carcinoma cervix with FIGO stages IIA-IIIB were randomized into two arms- cisplatin 40mg/m2/week for 5 weeks was given in control arm, whereas cisplatin 30mg/m2/week and paclitaxel 50mg/m2/week for 5weeks were given in study arm. The study arm showed a CR of 84%, compared with 75.6% in the control arm (P=0.4095). The median follows up results show better disease-free survival (DFS) in the latter (64.3% vs. 79.5%) and overall survival (78.6% vs. 87.2%). This prospective study concluded that there was potential benefit with the addition of paclitaxel to the standard regimen of concurrent cisplatin-based chemotherapy for carcinoma cervix, although the differences were not statistically significant. Cerrotta et al[16]. evaluated the feasibility of concurrent radiotherapy and paclitaxel administration. Complete response (CR) was reported in 63%. Out of 12 CR patients at the end of treatment, 10 maintained complete local remission for a median follow up of 47 months. In this study, the study arm (cisplatin + paclitaxel) showed CR in 63.3% of the cases in comparison to 67.7% of the control arm (cisplatin). Partial response was also numerically higher in the control arm (25.8% vs. 16.6%), but these differences were not statistically significant (P=0.406).Moore et al[17]. in a phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent or persistent squamous cell carcinoma of the cervix inferred objective responses to be 19% (6% complete plus 13% partial) of patients receiving cisplatin vs. 36% (15% complete plus 21% partial) receiving cisplatin + paclitaxel (P=0.002). They concluded that cisplatin +paclitaxel is superior to cisplatin alone concerning response rate and PFS with sustained quality of life.

Chen et al study where weekly paclitaxel was combined with 3 weekly cisplatin. The maximum tolerated dose (MTD) of this trial was reported as paclitaxel 50 mg/m2/week with cisplatin 50 mg/m2 once in 3 weeks. Pignata et al.[18] which reported cisplatin 30 mg/m2 and paclitaxel 50 mg/m2 as the MTD. both these studies reported tumour response rates more than 90%.

Disilvestro et al.[19] did study where cisplatin and paclitaxel where used as radio sensitizers in cervical cancer. The MTD reported was cisplatin 40 mg/m2/week and paclitaxel 40 mg/m2/week. This study reported a complete response.

In our study, at the completion of intracavitary brachytherapy, the complete response rate was numerically higher in cisplatin and paclitaxel group (88%). Compared to cisplatin group (74%). At 3-month partial response was more in control group (10%) and in study group was (7%) and at 6-month progressive disease was (5%) in study arm and (7%) in control group.

The complete response rates further improved in both groups, with the study group consistently showing a trend towards better response. However, no statistically significant differences were observed at these time points (p - >.05).

Moore et.al In this study, mild-to-moderate rectal toxicity was observed during treatment (within the first 8 weeks). It was significantly pronounced in the study arm: Grade II toxicity was observed in 17 patients (56.66%) against 8 in the control arm (25.8%). The P-value is 0.014 which is significant. The majority of the patients faced mild-to- moderate GI toxicity (22 out of 61, 36.06%), but for Grade II and above, GI toxicity was significantly more in the study arm (66.6% vs. 6%). The P-value is less than 0.001. About 10% of the study arm (paclitaxel + cisplatin) patients had Grade III hematological toxicity compared with 3% of the control arm (cisplatin only). But this difference was not statistically significant (P = 0.570). The nephrotoxicity profile was comparable in both the arms (P = 0.545). Skin toxicity was significantly more pronounced in the study arm (50% of the patients facing Grade II and above toxicity, P <0.001), likely attributable to the addition of paclitaxel as a radiosensitizer.Regarding late rectal toxicity, both the arms of the study were comparable, with only 6% of the study arm and 3% of the control arm patients experiencing Grade III toxicity (P = 0.623). Late bladder toxicity was numerically slightly higher in the study arm (20% vs. 16%), but all the cases were of Grade I toxicity and there was no statistical significance

for this difference (P = 0.694). Thakur. Et al In their phase III trial, observed an Increased in acute toxicities in the study arm in comparison to the control arm in terms of hematological grade II (35% vs. 12.2%), GI grade III (20% vs 7.4%), and GI grade IV (12.5% vs. 2.4%) toxicities.

Papadimitriou et al[20] showed grade III or IV hematological toxicities including anaemia in 18% of the patients and granulocytopenia in 15% of the patients treated with cisplatin + paclitaxel based chemoradiation. About 53% of the patients developed some degree of neurotoxicity; 21% of the cases were grade II or worse.

In our study, majority of patients faced mild to moderate gastrointestinal toxicity. Grade II diarrhoea and nausea & vomiting was more in study arm and (p - < .05). Grade 1 rectal toxicity was observed during treatment and it was significantly pronounced in the study arm. (p = .04). majorly patients faced grade II hematological toxicity was more in study arm compare to control group.

Grade III anaemia and neutropenia was observed 5% in study arm and 2% in control arm, but it was not statistically significant. Grade II skin toxicity was more in study arm (p- >.05). grade I cystitis was in increasing trend towards higher toxicity in study arm. but the differences were not statistically significant.

CONCLUSION

The study demonstrated that the addition of weekly Paclitaxel to weekly Cisplatin in concurrent chemoradiation for cervical cancer resulted in a numerically higher complete response rate The response of treatment in both groups was assessed by RECIST criteria (1.1), although this difference did not reach statistical significance. The combination regimen, however, was associated with a significantly higher incidence of Grade II acute toxicities, particularly gastrointestinal toxicities. Based on these findings, it can be concluded that while the addition of Paclitaxel may offer a potential benefit in terms of treatment response, this benefit needs to be weighed against the increased risk of toxicity. The choice of regimen should be individualized based on patient factors and the balance between potential benefits and risks.

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