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Original Research Article

Comparative Study of Conventional EBRT plus Concurrent Weekly Carboplatin versus Conventional EBRT plus Concurrent Weekly Paclitaxel in Locally Advanced Carcinoma Cervix

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Abstract

Background: For patients with early-stage cancer, radiotherapy (RT) or surgery are the mainstay of treatment. However, multimodality treatment approaches, such as RT combined with cisplatin-based chemotherapy (CT), neoadjuvant chemotherapy, or CT followed by radical surgery, have been shown to improve both disease-free and overall survival. Concurrent chemotherapy and radiation therapy (CCRT) is a recognised kind of treatment for locally advanced cervical cancer. For the treatment of locally advanced cervical cancer, radiation therapy has been combined with carboplatin, an equivalent of cisplatin with a similar mode of action.

Aims and Objectives: to compare the effects and side effects of weekly paclitaxel and concurrent chemotherapy with weekly carboplatin in locally advanced cervical cancer.

Materials and Methods: This study will cover all histopathologically confirmed patients with locally advanced cervical cancer (FIGO stage IB2-IVA) who registered at Govt. Cancer Hospital, Indore between April 2015 and April 2016. Two groups of randomly chosen patients, each with 30 patients, will be formed. One group received EBRT and concurrent inj. treatment. Second group receiving EBRT and concomitant paclitaxel 80mg/m2 IV weekly in addition to carboplatin 150 mg/m2. For a total of 35 days, EBRT will be administered using the parallel opposed (anterior posterior fields)/four field box approach. Following EBRT, 3 fractions of weekly intracavitary brachytherapy will be administered. Total duration of completion of treatment with EBRT and ICRT should be 56 days.

Results: Complete remission was 66.67% in the carboplatin arm and 56.67% in the paclitaxel arm. Compared to paclitaxel arm, carboplatin arm had a partial remission rate of 33.33%.

Conclusion: EBRT with concurrent weekly carboplatin has a better response than concurrent weekly paclitaxel and is associated with a more tolerable incidence of nausea and vomiting as well as less diarrhoea and skin sensitivity.

Keywords: Neoadjuvant chemotherapy, carboplatin arm, paclitaxel arm, cisplatin-based chemotherapy.

Introduction

Over 500,000 women worldwide suffer cervical cancer, making it the third most frequent cancer in women and the most common gynecologic cancer.[1] The disease is a leading source of morbidity and mortality worldwide, especially in underdeveloped nations, with 233,000 deaths per year. [2] The second-most populous nation in the world, India, was responsible for 26% (72,800) of cervical cancer fatalities. For patients with early-stage cancer, radiotherapy (RT) or surgery is the mainstay of treatment. However, multimodality treatment approaches, such as RT combined with cisplatin-based chemotherapy (CT), neoadjuvant chemotherapy, or CT followed by radical surgery, have been shown to improve both disease-free and overall survival. Concurrent chemotherapy and radiation therapy (CCRT) is a recognised kind of treatment for locally advanced cervical cancer.

Brachytherapy and external beam radiotherapy are currently the two main radiation treatment procedures. While central disease (cervix, vagina, and medial parametria) is typically treated with intracavitary sources, EBRT is used to treat the entire pelvis and the parametria, including the common iliac and para-aortic LN. [3,4]

In comparison to radiotherapy alone, several trials have demonstrated the superiority of platinum-based therapy combined with radiation. The concurrent administration of radiation and weekly cisplatin may be regarded as a fair standard of care based on these presumptions. Nevertheless, the cure rates for locally advanced squamous cell carcinoma have stagnated in recent years, despite the advantages of adding platinum-based chemotherapy. [5,6] There is a high likelihood of metastasis and recurrence, and treatment outcomes are less than ideal.

The chemotherapeutic medication paclitaxel, a taxane, has been discovered to have significant activity in solid tumours, particularly epithelial ovarian cancer, lung, and breast cancer.[7] In human cervical cancer cell lines, preclinical investigations have demonstrated that paclitaxel has a radio sensitising effect.[8,9] Additionally, it has been demonstrated that this medication has a preferential cytotoxic effect on human cervical cancer cells with reduced Raf-1 kinase activity, making it attractive to use it with radiotherapy.[10] Phase I trials examined the clinical viability of radiation therapy and paclitaxel given concurrently and established a maximum tolerated dose (MTD) of 50 mg/m2 per week.[11,12] In addition, the clinical efficacy of paclitaxelhas been tested in phase II and III studies for metastatic and recurrent cervical cancer with objective response rates ranging between 36% and 47%.[13-16]

Comparing carboplatin to cisplatin reveals that it is significantly less emetic and has lower levels of nephrotoxicity and neurotoxicity.[17,18] When compared to cisplatin, this drug's favourable toxicity profile may help patients stick to their treatment plans more closely.

Material and Methods

This study would involve 60 histopathologically confirmed patients with locally advanced cervical cancer (FIGO stage IB2-IVA) who were registered at the Govt. cancer hospital in Indore between

April 2015 and April 2016. A total of 60 randomly chosen patients will be split into two groups, 30 in each group. A patient won't be given a priority bias and the criteria used to sort them will be chosen at random.

Inclusion criteria

- Histopathologically proven locally advanced Squammous cell Carcinoma cervix (FIGO stage IB2-IVA).
- Age of patient up to 70yrs.
- ECOGperformancestatus0-1-2.
- Informed consent

Exclusion criteria

1. Haematological, cardiac, renal or liver function abnormalities.
2. Hypersensitivity to Paclitaxel/Carboplatin
3. Distant metastasis i.e. Stage IVB.
4. Prior Radiotherapy.
5. Prior Chemotherapy.
6. Other synchronous malignancies.
7. Prior Surgery
8. Connective tissue disorder

Radio therapy treatment protocol schedule (Both Arms)

Patients will be planned for External Beam Radiotherapy delivered by Co^{60} teletherapy machine (Theratron780E) and HDR brachy therapy. Cases will be treated by conventional radiotherapy schedule as follows:

EBRT	=	4600cGy
HDRICBT	=	700cGyX3 # point A
Total Dose	=	6700 cGy in point A.

After 35 days of EBRT, which will be administered five days a week, three fractions of weekly intra cavitary brachytherapy will be administered. The entire course of EBRT and ICRT treatment should take 56 days to complete.

Parallel opposed (anterior-posterior fields)/four field box methods are the portals for pelvic EBRT.

Concurrent Chemotherapy protocol schedule:

1. **Arm A**: (control group) - Inj. Carboplatin 150 mg/m2 IV weekly with Conventional EBRT

This group will receive weekly injections of carboplatin 150 mg IV in 300 ml NS over an hour, chosen at random from patients who have never been treated before. Dexamethasone 8 mg, Omez 20 mg, and a 5HT3 receptor antagonist as an antiemetic are used as premedications, along with fluids for two hours before and after chemotherapy.

2. **Arm B**: (study group)-Inj.Paclitaxel 80mg/m2 IV weekly with conventional EBRT

Patients in this group who were not previously treated would receive weekly doses of Paclitaxel 80mg/m2 IV in 300ml NS over the course of an hour. Dexamethasone 8 mg, Omez 20 mg, and a 5HT3 receptor antagonist as an antiemetic are used as premedications, along with fluids for two hours before and after chemotherapy.

Pre-treatment Evaluation:

Complete history and general physical examination with an assessment of the patient's performance. Systemic examination, Pelvic examination will be done.

Complete blood count, renal function, liver, and serum electrolyte tests are among the laboratory tests that are performed.

Imaging tests such chest x-rays (PA view), pelvic and abdomen USGs, and pelvis and abdomen CT/MRIs (as needed) will also be performed.

Observation during Radiotherapy

Patients in the trial group and the control group will be checked on a weekly basis for local disease response and the emergence of unfavourable responses such diarrhoea, skin or mucosal reactions. Diarrhoea and mucosal responses will be graded in accordance with WHO standards.

Doses at which patients develop adverse reactions will be noted in both control & study group. Haematological & renal function test will be evaluated weekly during treatment. Patient with anaemia will receive necessary blood transfusion, and those with deranged renal parameters will receive adequate hydration prior to chemotherapy. Symptomatic treatment will be given in patients suffering from side effects of chemoradiotherapy. Split of maximum of 25 days may be given for radiotherapy side effects and gap correction will be done, if needed.

Analysis and comparison of the research groups' findings with the control group will be done in terms of things like side effects, drug toxicity profiles, tumour responses, and the presence or absence of local illness. In order to analyse the data, Kruss-Wallis and the Chi-Square test for co-relation will be used.

Evaluation following treatment completion and follow-up: The patient will be assessed at the conclusion of therapy as well as at the first, third, and sixth month check-ups by PS/PV and local examination in the presence of female nursing staff. Responses will be scored as either a Complete Response (CR) or a Partial Response (PR).

Results and Discussion

Table1: Age wise distribution of the cases

Age (in Years)	Study (P)(%)	Study (C)(%)
30-39	5(16.67%)	7(23.33%)
40-49	9(30%)	10(33.33%)
50-59	8(26.67%)	8(26.67%)
60-69	6(20%)	4(13.33%)
>70	2(6.66%)	1(3.33%)
Total	30	30

Table 2: Performance status

ECOG	Study (P) (%)	Study (c) (%)
1	28(93.33%)	26(86.66%)
2	2(6.6%)	4(13.333%)
Total	30	30

Table 3: Stage of disease (Figo)

Stage of Disease	Study(P) (%)	Study(c) (%)
IIA	4 (13.33%)	2(6.67%)
IIB	13(43.33%)	7(23.33%)
IIIA	4(13.33%)	5(60%)
IIIB	8(26.67%)	14(46.67%)
IVA	1(3.33%)	2(6.67%)
Total	30	30

Table 4: Distribution of cases as per the histology

Tumor Differentiation	Study(P) (%)	Study(c) (%)
SCC	29 (96.67%)	30 (100%)
ADENO	1 (3.33%)	0 (0.00%)
Total	30	30

Table 5: Distribution of the Cases according to renal function

Blood Urea	Study (P) (%)	Study (c) (%)
Normal	29	30
Abnormal	1	0
Total	30	30

Table 6: Response to Treatment

Response To Treatment	Study (P) (%)	Study (c) (%)
CR	17(56.67%)	20(66.67%)
PR	13(43.33%)	10(33.33%)
Total	30	30

This table depicts the finding according to response to treatment. In carboplatin study arm 20 (66.67%) cases were observed with complete response and 10 (33.33%) cases were having partial response, In. paclitaxel study arm 17 (56.67%) case were showed complete response and 13 (43.33%) cases were showed partial response. While in the control arm 10 (33.33%) cases were found with complete response and 20 (66.67%) with partial response and statistically the complete response in the study arm was significantly higher.

The results of the chi-square test, which were used, showed that the carboplatin arm of our study had a more comprehensive response than the paclitaxel study and control arm, with a value of 7.04 and a P value of 0.029.

The use of cisplatin in chemoradiation regimens for the treatment of locally advanced cervical carcinoma has been the standard of care in the United States since 1999, but in spite of using cisplatin alone for concurrent chemoradiation, the number of patients achieving complete response from the disease was low.[16] And many cases tend to show residual or recurrence at pelvic or the distant sites. This has led to investigate other drugs for concurrent

chemoradiation. In our study paclitaxel and carboplatin was chosen in place of cisplatin for concurrent chemoradiation.

In human cervical cancer cell lines, studies have revealed that paclitaxel has a radio-sensitising effect.[8,9] Phase I trials examined the clinical viability of paclitaxel and radiation therapy given concurrently, and they determined a maximum tolerated dosage (MTD) of 50 mg/m2 per week.10-12 In addition, phase II and phase III studies on metastatic and recurrent cervical cancer have evaluated the therapeutic efficacy of paclitaxel, with objective response rates varying between 36% and 47%.[13-15]

Compared to cisplatin, carboplatin is less toxic and more tolerable. Other solid tumours, such as non-small-cell lung cancer and head and neck cancer, have been treated with chemoradiation using carboplatin. The majority of the patients in the population under study had Grade 1 ECOG performance status. Patients either showed discharge P/V or bleeding per vaginal symptoms. Our analysis revealed that >90% of the cases documented in either arm belonged to people of lower socioeconomic standing. This may be because there is a higher prevalence of cervical cancer among the lower socioeconomic classes due to unsanitary living conditions, potential HPV infections, or other STDs that could possibly act as an etiological agent.

Almost all the cases enrolled in the study were from rural area, and majority of the cases were tobacco consumers in one term or other. This might be due to their illiteracy and lower education level in the rural areas.

Two patients in the control arms and one patient in paclitaxel study arm had a raised urea and creatinine values. This patient was admitted and was adequately hydrated to normalize the renal function parameters.

Cases registered for the study were mostly from II B to III B stages. In a control arm there were maximum 12 patients in III B, in paclitaxel study arm there were 13 patient in II B and in carboplat in study arm there were 14 patients in III B. 28 and 2 patients out of 30 were squamous cell carcinoma and adeno carcinoma respectively, In paclitaxel study arm 29 and 1 patients were squamous cell carcinoma and adenocarcinoma respectively, all cases in carboplatin study arm were squamous cell carcinoma.

Skin Reactions

Most patients developed skin reactions during the 4^{th}, 5^{th} and 6^{th} week of treatment. It was found that the incidence of skin reactions was more in the paclitaxel study population with most of the cases reporting with grade 1 skin reactions during the course of treatment. The incidence of skin reaction was lower in the control arm as compared to study arm.

According to the results of the Krusswallis test, carboplat and paclitaxel show skin reactions that are more severe in the fourth and fifth weeks of treatment, respectively. Desquammous-type reactions predominated in the field of irradiation, and they were characterised by excruciating itching. Oral antihistamines and gentian violet were used to treat it. By the end of the radiation treatment, the desquamation had reduced, and by the second month after the whole course of treatment, a new epidermal layer had developed. Eight patients experienced cutaneous reactions unrelated to radiation. The majority of the skin reactions that occurred outside of the irradiation zone were acne-like and primarily affected the face and nasolabial fold. They were treated with oral antihistamines and topical emollients. In control arm the incidence of skin reaction was comparatively lower.

Upper GI Side Effects

The carboplatin study arm had the highest incidence of nausea and vomiting cases, with the majority of cases reporting grade 1 or grade 2 nausea and vomiting within the first four weeks.

Grade III vomiting patients were hospitalised and treated with intravenous fluids and oral rehydration solutions. As no chemotherapy was administered in this patient who had no evidence of cancer and reported experiencing nausea or vomiting of grade III, the incidence of nausea and vomiting was noticeably lower in the control group.

Lower GI Side effects:

With the majority of patients experiencing grade I diarrhoea in the second, third, and fourth weeks of treatment, it was found that diarrhoea was the most common and dangerous side effect of patients in the study arm, more so in the paclitaxel arm than the carboplatin arm.

When comparing radiation with concurrent weekly cisplatin or weekly paclitaxel in patients with advanced cervical cancer, Fady B Geara et al. discovered the similar result [20]. More patients present with diarrheas side effects in the paclitaxel group (53%vs. 37%). Patients presenting with grade II and grade III diarrhea were brought to the ward and treated symptomatically. We performed a stool culture and sensitivity test on these patients, and the results showed that the stool sample was sterile. Those who presented with grade I diarrhoea were treated with probiotics and anti-motility medications. A daily maximum dose of Tab loperamide up to 10 mg was administered together with a probiotic. In 5 patients in the paclitaxel trial arm, radiation was administered without paclitaxel because of a greater frequency of diarrhoea.

Less than 10% of cases in the other arms of treatment presented with complaints of burning urination fever, and their routine urine analysis indicated urine sample laden with pus cells, but 30% of patients in the paclitaxel arm did. The patients had a urinary tract infection, and they responded for five days to the broad-spectrum intravenous antibiotics Ciprofloxacin and metronidazole. Chemotherapy or radiation treatments may increase the risk of urinary tract infections. Peripheral neuropathy has been seen in two patients from the paclitaxel arm.

Response to treatment

Pragyat Thakur et al [19] when evaluate the benefit with the addition of paclitaxel to cisplatin-based concurrent chemoradiotherapy (C-CRT) for the treatment of locally advanced carcinoma of the uterine cervix found enhanced outcomes in study group (paclitaxel and cisplatin) over the control arm (cisplatinonly) in terms of DFS (79.5%vs.64.3%;P=0.07) and OS (87.2%vs.78.6%;P=0.27). In our study, it was shown that only 17/30 patients in the paclitaxel study arm had a full response, making it inferior to the carboplatin arm. The same outcomes are provided for the paclitaxel arm by Fady B Geara et al [20]. According to their statistics, the overall response and progression-free survival rates with paclitaxel, which is the experimental arm, are not better than those with cisplatin. The patients in our study were followed up for 6 months. It was found that 1 patient from paclitaxel study arm had recurrence. With a total of 60 patients giving consent for the study. The data analyzed after the study clearly showed the benefit of concurrent chemoradiation. Chi-square test applied and its value was 7.04, with P value 0.029, shows that our study is significant with carboplatin in arm has more complete response as compare to paclitaxel study. The recurrence was low in study arm compared to control

arm and the side effects were easily manageable.

Conclusion

We have conducted a trial of concomitant chemotherapy with paclitaxel in one arm and concomitant carboplatin in another arm for advanced carcinoma of cervix in 60 patients in 2 arm of 30 -30 patients at government cancer hospital with the following end results

1. It was that in the carboplatin study arm 66.67% of patients showed complete response, in paclitaxel arm 56.67% of patients showed complete response.
2. A higher incidence of diarrhea and skin reaction was noted in the paclitaxel study group as compared to carboplatin study arm.
3. A higher incidence of nausea and vomiting were seen in the carbo platin-study arm.
4. It was seen that early adverse events that occurred with concurrent chemoradiation was mostly grade 1, which was easily manageable.
5. Late complication could not be evaluated in this short duration of study. It requires along follow-up and greater compliance.
6. The compliance of patients in the control arm was better than that the study arm.

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