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A prospective comperative study of cisplatin vs carboplatin based concurrent chemoradiation in locally advanced carcinoma cervix

K Pawan[1], Sandeep Jain[2*], RS Gothwal[3], Shantanu Sharma[3], Pradeep Naik E[1]
[1] Resident, Department of Radiotherapy, SMS Medical College, Jaipur, Rajasthan, India
[2] Sr. Professor, Department of Radiotherapy, SMS Medical College, Jaipur, Rajasthan, India
[3] Professor, Department of Radiotherapy, SMS Medical College, Jaipur, Rajasthan, India

Abstract
Aim: To evaluate treatment outcomes of locally advanced cervical cancer patients who received concurrent weekly Carboplatin or Cisplatin with radiation therapy.
Methods and Materials: This study is a prospective analysis of 180 patients with cervical cancer stage IIB-IVA who were treated at our centre. Ninety patients in each arm received concurrent CTRT with weekly cisplatin or Carboplatin followed HDR-ICBT. Primary endpoint was the acute toxicities; whereas secondary endpoints were overall response rate, which includes complete and partial responses.
Results: The treatment was well tolerated. Anaemia, nausea vomiting, neutropenia nephrotoxicity and bladder toxicity was more frequently occurred with weekly cisplatin and were statically significant ((P<0.05). Grade 1 thrombocytopenia was seen in more frequently with Carboplatin which was statically significant. Nephrotoxicity was limited to cisplatin arm and 13.4% & 23.3% patients developed grade 1 & grade 2 nephrotoxicity which was statically significant (P<0.001). Complete response was present in 67.8% & 66.7% patients in cisplatin and Carboplatin arm respectively which was progressed to 87.8% and 83.3% after 6 months of follow up. Disease progression was noted in 8.9% & 13.4% patients in respective arms.
Conclusion: Concurrent weekly Carboplatin with radiation therapy yields high response rate with have similar toxic in locally advanced cervical cancer. Carboplatin may be feasible alternative treatment with minimal toxicities in patients who have contraindication for cisplatin.

Keywords: carcinoma cervix, concurrent chemoradiotherapy, cisplatin, carboplatin

Introduction

In India, cervical cancer accounts for almost 14% of all female cancer cases and account second most common cancer in females [1].

Worldwide, Cancer cervix ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women [2]. Treatment of choice for most patients with locally advanced disease is radiation therapy using a combination of external beam irradiation and brachytherapy. Weekly cisplatin at with a dose of 40 mg/m2 concurrent to RT is widely accepted as the standard regimen of concurrent chemoradiotherapy. Five randomized phase III studies and one meta-analysis showed the benefit of adding cisplatin-based chemotherapy to radiotherapy (RT) for the treatment of locally advanced CC in terms of overall survival (OS) and overall response rate (ORR) [3-7]. Nephrotoxicity is often a major concern in some patients with locally advanced cervical cancer that are not eligible to receive cisplatin, due to comorbidities such as postrenal kidney injury secondary to pelvic mass.

No phase III studies have compared the equivalency of Carboplatin to cisplatin concomitant with RT or the superiority of cisplatin. The use of Carboplatin, therefore, is supported by small phase I and II studies and pre-clinical evidence with RT [8, 9]. The objective of this study is to evaluate the results of treatment with cisplatin or Carboplatin concomitant with RT in cases of locally advanced cervical cancer patients.

Methods and Materials

The study includes a prospective analysis of 180 SFIGO stage IIB-IVA, cervical cancer patients treated with concurrent chemoradiotherapy ICBT in a tertiary care center of north- west India between May 2019 and April 2020. After approval of institutional Review Board/ Ethical committee, histopathological proven confirmed squamous cell carcinoma of cervix patients who required concurrent chemoradiotherapy ICBT and ready to give informed written consent were included in this study. Ninety patients in each arm are required as sample size for present study at 80% study power and Alpha error of 0.05. Patients were divided in two arms. Arm A (Carboplatin based concurrent chemoradiotherapy) and Arm B (Cisplatin based concurrent chemoradiotherapy). Patients with previous history of cervical irradiation or with history any co-morbidity were excluded from study population.

Evaluation

Before initiation of the treatment, all patients underwent complete physical examination and biochemical investigations. During CTRT acute toxicities were scored according to the RTOG and common terminology criteria for adverse events (CTCAE Version 3.0) criteria of acute toxicities in both groups of patients. Response evaluation was done at the completion of ICBT, 3 months, 6 months in both Arms A & B based on clinical examination and CT Abdomen in each patient. Patients will then be categorized as per Response Evaluation Criteria in Solid Tumours

Criteria (Response Evaluation Criteria in Solid Tumours Version1.1).

In weekly chemotherapy, cisplatin was given at a dose of 30 mg /m2 and Carboplatin at a dose of area under curve AUC=2. In radiotherapy, all patients were treated over BHABHATRON – 2 Cobalt60 Machine in supine position with immobilization using four field technique with EBRT of 50Gy were delivered in 25 fractions, 2Gy per fraction in both the groups. After one week gap of completion of CTRT, HDR-ICBT was given at a Total dose of 21Gy in 3fractions, 7 Gy per fraction. The plan of the treatment were to prescribe total dose of 85-90 Gy at point A. Dose calculations for rectum and bladder was made according to the ICRU—38 recommendations.

Results

In this prospective, randomized clinical study median age at presentation was 49.7 and 51.2 years in Cisplatin and Carboplatin arm respectively with a range of 29-70 years. Majority of population was in 5th decade of life. Thirteen percent of the population was having age less than 40 years. Moderately differentiated squamous cell carcinoma was most common histological subtype with a frequency of 51.4%. In the present study, 58% patients were from rural background while 42% were from urban background, mostly having ECOG performance scale of 0 & 1 and hemoglobin level between 10-12 gm%. Ulceroproliferative morphology was associated with majority of patients. In FIGO Stage IIB (49.1%) was common disease stage followed by IIIA stage (26.2%)

Patients' characteristics are shown in Table-1.

Table1: Patients' Characterstics

Characterstics	Cisplatin Arm	Carboplatin Arm
Age		
Mean±SD	49.69 ± 9.08	51.19 ± 7.70
ECOG score		
0	47(52.2%)	36(40%)
1	35(38.9%)	45(50%)
2	8(8.9%)	9(10%)
Socioeconomic Status		
Low	63(70%)	65(72.2%)
Middle	27(30%)	25(27.8%)
Background		
Rural	53(58.9%)	51(56.7%)
Urban	37(41.1%)	39(43.4%)
FIGO stage		
IIB	14(15.5%)	13(14.4%)
IIIA	43(47.8%)	45(50%)
IIIB	20(22.2%)	19(21.1%)
IIIC	4(4.4%)	3(3.3%)
IVA	3(3.3%)	3(3.3%)
Tumour size		
<4 cm	29(32.2%)	31(34.4%)
>4 cm	61(67.8%)	59(65.6%)
Histopathology		
WD SqCC	53(58.9%)	51(56.6%)
MD SqCC	30(33.3%)	29(32.2%)
PD SqCC	7(7.8%)	10(11.1%)
Hb level at baseline		
>10gm%	51(56.6%)	53(58.9%)
<10 gm%	39(43.3%)	37(41.1%)

In the present study anaemia was more prevalent with cisplatin arm. During 3rd, 4th & 5th week grade 1 was present in 22.2% & 15.5% patients in Cisplatin and Carboplatin arm respectively. Grade 2anaemia was present in 15% % 6% in respective arm (p_<0.05). Grade 2 and grade 3 neutropenia was collectively present in 3.6% cases in both arm and was not statically significant. Eighteen percent patients in cisplatin arm developed grade 1 neutropenia (18.5% vs 3.7%) and was statically significant(p P<0.001) Grade 1 thrombocytopenia was seen in Carboplatin arm which was statically significant. Thirteen patients (7.2%) in Carboplatin arm and five patients (2.7%) in cisplatin arm developed grade 1 thrombocytopenia (p<0.029).

Nausea vomiting and nephrotoxicity was more frequently occurred in cisplatin arm. During 1st week grade1& grade2 nausea vomiting was present in 23.3% vs 4.5% patients in Cisplatin and Carboplatin arm respectively which was statically significant (P<0.001). During chemoradiotherapy course 9 patients (10%) in cisplatin arm and 1 patient (1.2%) developed bladder toxicity which was statically significant (p=0.032). Grade 1 & grade 2 nephrotoxicity was limited to cisplatin arm. During radiotherapy course 13.4% & 23.3% patients developed grade 1 & grade 2 nephrotoxicity in cisplatin arm respectively. (P<0.001). There was no statistically significant toxicity between the study group and control group for acute skin reaction and acute diarrhea.

After the completion of ICBT, patients were evaluated for response. Complete response was present in 67.8% & 66.7% patients in Cisplatin and Carboplatin arm respectively while partial response was present in 31.1% & 32.2% patients respectively. After 3 month of ICBT partial response decreased up to 10% & 7.8% while progressive disease was noted in 6.7% & 10% patients in Cisplatin and Carboplatin arm respectively. At 6 months of follow up 87.8% and 83.3% patients showed complete response while 8.9% & 13.4% patients noted with disease progression in Cisplatin and Carboplatin arm respectively.

Discussion

Based on the results from the original studies of the Gynecologic Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG), concurrent cisplatin-based with radiation therapy has been widely used as the standard treatment as adjuvant postoperative therapy for early stage cancer with risk factors and as primary treatment for locally advanced cervical cancer patients [3-7]. Major side effects of concurrent cisplatin or cisplatin/ 5-FU with radiation therapy were observed, particularly nephrotoxicity. The more commonly used regimen is weekly cisplatin at a dosage of 40 mg/m2 with radiation treatment which was found to have lower toxicity than the 3-weekly dosage [10]. To avoid the unfavorable side effects and toxicities of cisplatin especially in those with poor preserved renal function, Carboplatin was commonly used in our institution. We used weekly Carboplatin at a dose of 100 mg/m2 as a radiation sensitizer in patients with normal renal function or at AUC2 in those with impaired renal function as had been recommended and also used in this study.

Carboplatin has lower toxicity and is better tolerated than cisplatin. It could be administered even to patients with renal compromise, not an uncommon occurrence in patients with locally advanced cervical carcinoma. In our study anaemia, neutropenia, nausea vomiting, nephrotoxicity and bladder toxicity were more consistent with cisplatin arm. During 3rd, 4th & 5th week grade 1 was present in 22.2% &

15.5% patients in Cisplatin and Carboplatin arm respectively. Grade 2anaemia was present in 15% % 6% in respective arm (p_<0.05). Grade 2 and grade 3 neutropenia was collectively present in 3.6% cases in both arm and was not statically significant. Eighteen percent patients in cisplatin arm developed grade 1 neutropenia (18.5% vs 3.7%) and was statically significant(p P<0.001) Grade 1 thrombocytopenia was seen in Carboplatin arm which was statically significant. During 1st week grade1& grade2 nausea vomiting was present in 23.3% vs 4.5% patients in Cisplatin and Carboplatin arm respectively which was statically significant (P<0.001). Grade 1 & grade 2 nephrotoxicity was limited to cisplatin arm. During radiotherapy course 13.4% & 23.3% patients developed grade 1 & grade 2 nephrotoxicity in cisplatin arm respectively [(P<0.001), (Figure:1)].

Thrombocytopenia was only toxicity that was more significantly associated with Carboplatin. Thirteen patients (7.2%) in Carboplatin arm and five patients (2.7%) in cisplatin arm developed grade 1 thrombocytopenia [(p<0.029), (Figure: 2)].

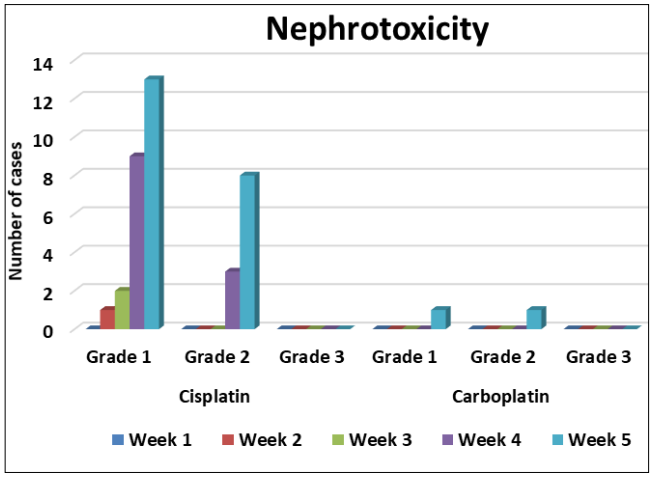

Fig 1: Nephrotoxicity

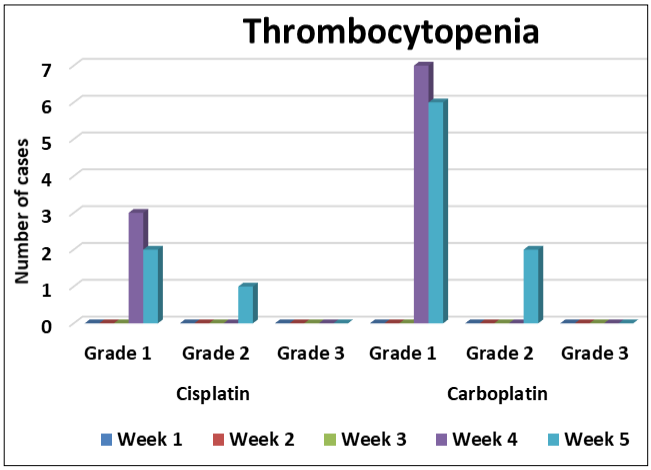

Fig 2: Thrombocutopenia

Several phase I and phase II trials of patients with locally advanced cervical carcinoma treated with radiation therapy and concurrent carboplatin have shown minimal toxicity. *Corn et al* [11]**.** Reported 15 patients treated with chemoradiation using carboplatin at a dose of 90mg/m2. None of them had any grade 3 or grade 4 toxicity. *Katanyoo et al* [12]. Found only grade 1–2 toxicities: 28.4% for hematologic and 39.2% for non-hematologic toxicities. Regarding hematologic toxicities; 23.7%, 5.1% and 2.7% of patients experienced anemia, neutropenia, and thrombocytopenia, respectively. For nonhematologic toxicities; symptoms of nausea, vomiting, dysurea, and diarrhea were reported in 9.4%, 8.1%, 2.7%, and 35.8% of patients, respectively. In a study by *Duenas-Gonzalez et al* [9]. Identified the suitable doses of Carboplatin with standard pelvic RT. At 116 and 133 mg/m2, respectively, no Grade 4 toxicity occurred. *G. Rao et al* [13]. in a study with weekly paclitaxel and Carboplatin with EBRT and concluded that the combination of paclitaxel with carboplatin, instead of cisplatin, is advantageous because of lower renal and gastrointestinal toxicity at the expense of more hematologic toxicity. *Higgins et al* [14]. Reported 31 cervical cancer patients treated with CTRT (weekly concurrent Carboplatin at an AUC of 2). Only three patients developed grade 3leucopenia, one patient developed grade 3 neutropenia, and two patients developed grade3 thrombocytopenia. *Muderspach et al* [15]. Reported only 4 patients with grade 3 toxicity (two patients had anemia, one neutropenia, and one patient with urinary toxicity). A retrospective search of databases by *N. Moore et al* [16]. Finding raises the possibility that combination carboplatin and paclitaxel may actually be superior to combination cisplatin and paclitaxel with acceptable toxicities. *A. Dubay et al* [8]. In a retrospective study with concurrent Carboplatin, found 9% grade 1 and 5% grade 2 thrombocytopenia. Six patients (29%), two patients (9%), and two patients (9%) experienced grades 1, 2, and 3 granulocytopenia, respectively. Two patients (9%), three patients (14%), and two patients (9%) experienced grades 1, 2, and 3 anemia, respectively. No renal toxicity was observed. *Rose et al* [17]. Observed, with Carboplatin, toxicities were minimal, with less than 2% haematological toxicities. *Xue R et al* [18]. Found the rates of toxicities ≥ grade 3 appeared to be similar between these two regimens, compared with Cis-RT, Car-RT was associated with more thrombocytopenia ≥ grade 3 (9.8% vs. 2.1%). The most common non-hematological toxicities of Car-RT were nausea (or vomiting) and diarrhea, but significant toxic events were rare. The mean rate of nausea (or vomiting) ≥ grade 3 was 0.1% (reported in 8 studies; range from 0% to 1%), and the mean rate of diarrhea ≥ grade 3 was 0.1% (reported in 9 studies; range from 0% to 1%).

Similarly *Tharavichitkul et al* [19]. found that the acute toxicities as anemia, neutropenia and renal toxicity were more prevalent with cisplatin than Carboplatin. No difference was observed in thrombocytopenia, radiation dermatitis, proctitis or cystitis.

Nam J et al [20]. conducted a head to head comparison of carboplatin and cisplatin-based concurrent chemoradiotherapy in locally advanced cervical cancer patients with morbidity risks and as expected with carboplatin, thrombocytopenia was more common in the CarboRT group, although the difference was not statistically significant (p _.24). Specifically, grade 3–4 thrombocytopenia was noted in five patients (9.8%); and nausea, vomiting, and fatigue was tended to occur more in the CisRT group.

After the completion of ICBT, patients were evaluated for response. Complete response was present in 67.8% & 66.7% patients in Cisplatin and Carboplatin arm respectively while partial response was present in 31.1% & 32.2% patients

respectively. After 3 month of ICBT partial response decreased up to 10% & 7.8% while progressive disease was noted in 6.7% & 10% patients in Cisplatin and Carboplatin arm respectively.

At 6 months of follow up 87.8% and 83.3% patients showed complete response while 8.9% & 13.4% patients noted with disease progression in Cisplatin and Carboplatin arm respectively. (Table: 2)

Table 2: Response Evaluation

Duration	Cisplatin Arm			Carboplatin Arm		
	CR	PR	PD	CR	PR	PD
At completion of ICBT	61(67.8%)	28(31.1%)	1(1.2%)	60(66.7%)	29(32.2%)	1(1.2%)
After 3 Month	75(83.3%)	9(10%)	6(6.7%)	74(82.2%)	7(7.8%)	9(10%)
After 6 Month	79(87.8%)	3(3.4%)	8(8.9%)	75(83.3%)	3(3.4%)	12(13.4%)

Katanyoo et al [12]. Found similar result at 6 months of follow up. Complete response was achieved in 142 patients (95.9%) while six (4.1%) had persistent diseases. In regard to the response to treatment *Duenas-Gonzalez et al* [9]. Found 18 patients (75%) achieved complete response, 2 patients had progression, and 4 had disease persistence with a median follow-up of 8 months (range 4–15. *Micheletti et al* [21]. Reported a Phase I-II study of RT plus continuous infusion of Carboplatin and a complete response was obtained in 75% of patients. With a median follow-up of 9 months *Moore N et al* [16]. Reported a 21% complete response, 25% had a partial response, 27% had stable disease and 27% experienced disease progression with carboplatin. In a similar study by *Cetina L et al* [22]. Complete responses were achieved in 72 (84.7%) patients, whereas 5 patients (5.8%) had persistent and 8 (9.4%) progressive disease. *Xue R et al* [18]. In a Meta-analysis, the data showed marked heterogeneity, and thus a random-effects model was chosen. The pooled CR rate was 81% vs 79% for cisplatin and Carboplatin respectively (95% CI 0.74–0.89, I2 = 89%).

Similarly at 3 months after complete treatment *Veerasarn et al* [23]., found no significant difference in complete response (CR) rates control and study group *Nam J et al* [20].found complete RRs of 50.0% in the CarboRT group and 62.5% in the CisRT group. There were no differences in the overall RRs between the CarboRT and CisRT groups (90.0% and 87.5%, respectively; *p*_.31). *M. Sebastia˜o et al* [24]. reported a overall response rate of 95.3% cis-RT vs 95.4% carbo- RT (p = 0.911).

In the present study the tumor response was not statistically significant; complete response was slightly more in cisplatin arm. A possible explanation can be defined in the terms of cisplatin peak concentration during radiotherapy. The response to treatment was also found to be better in patients with hemoglobin more than 10 gm % as compared to those with hemoglobin less than 10 gm %.

The response to treatment was also found to be better in patient with well differentiated histopathology as compared to poorly differentiated histopathology of primary tumor as it is more responsive to radiotherapy and in those patients with better compliance to treatment. These parameters correlate well with studies done by *Takafumi Toita et al* [25]. and *J Vandana et al* [26].

Conclusion

Cisplatin-based concurrent chemoradiotherapy accepted as the standard regimen of concurrent chemoradiotherapy but nephrotoxicity is often a major problem with cisplatin in this patient population who often present with varying degrees of renal obstruction from local tumor extension. Weekly Carboplatin in concurrent with radiation therapy is feasible and convenient in cervical cancer patients. The treatment outcomes are comparable to other reports using weekly cisplatin (40 mg/m2) whereas the toxicities are less. This particular benefit of Carboplatin, especially in cervical cancer patients who frequently have some degree of renal function impairment makes Carboplatin's administration an attractive, safe and effective alternative to cisplatin.

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