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Original Research Paper

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CONCURRENT WEEKLY CISPLATIN VS TRIWEEKLY CISPLATIN WITH RADIOTHERAPY FOR TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER

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ABSTRACT

Introduction- The present study was conducted to assess the efficacy and toxicity profile of concurrent weekly cisplatin dosing as compared to 3 weekly cisplatin with radiotherapy in patients of cervical cancer and also to evaluate the compliance among them.

Methodology- This was prospective randomized comparative study at tertiary centreon patients of locally advanced cervical cancer. Patients were randomly divided into 2 groups and patients of group 1 received EBRT with weekly cisplatin whereas patients of group 2 received EBRT with 3 weekly cisplatin. All the patients were followed up for assessment of compliance, acute toxicities and treatment response.

Results- The study included 80 patients which were randomized into 2 groups. The population in two groups was comparable in baseline characteristics. No statistically significant difference in occurrence of acute toxicities between the participants of two groups was observed ($p>0.05$). Clinically, complete response was noted in 82.5% and 90% patients in group 1 and group 2 respectively. However the observed difference in response was not statistically significant ($p>0.05$).

Conclusion- The present study documented similar response and toxicity profile of both the regimens and thus concurrent weekly or 3 weekly cisplatin along with radiotherapy can be used with equal effectiveness in the treatment of cervical cancer.

KEYWORDS : Concurrent cisplatin, weekly, triweekly, central India, Cervical cancer

INTRODUCTION

According to World Health Organization, worldwide cervical cancer is the fourth most common cancer among females and the disease burden is estimated to be 570,000 new cases in 2018 i.e. attributing to 6.6% of all female cancers and leading to approximately 311000 deaths in 2018.[1,2] The age standardised incidence of cervical cancer was estimated to be 13.1 per 100000 women globally and the incidence is different in different countries ranging from less than 2 to 75 per 100000 women.[2] The occurrence of new cases of cervical cancer in India was reported to 106000 and contributing to 60000 deaths.[2]

Cervical cancer is the major public health problem affecting middle-aged women, particularly in low and Middle income countries.[2] Usually the cases with cervical cancer have favorable prognosis if diagnosed and treated in early stage with estimated 5 year survival rate of 80-90%. However, advanced disease are associated with poor prognosis.[3] Current treatment for locally advanced cancer cervix where surgical treatment is not indicated include cisplatin-based concurrent chemoradiation (CRT) based on five randomized trials.[4,5,6,7,8,9] Weekly cisplatin in a dose of 40 mg/m^2 is the most widely accepted standard regimen of CRT because of its convenience, equal effectiveness, and favorable toxicity in comparison to other 5-FU combined regimens.[10] However, various trials[11,12,13] have used 3 weekly cisplatin in a dose of 75–100 mg/m^2 as this form of chemotherapy is easy to administer and is associated with better patient compliance. The present study was conducted to assess the efficacy and toxicity profile of concurrent weekly cisplatin dosing as compared to 3 weekly cisplatin alone with radiotherapy in patients of cervical cancer and also to evaluate the compliance among them.

METHODOLOGY

The present study was conducted as a prospective randomized comparative study at Sanjay Gandhi memorial hospital Shyam shah medical College Rewa, for a period of 1 year i.e. from 1st April 2018 to 31st March 2019. The inclusion criteria of the study were patients with histopathologically proven locally advanced Squamous cell carcinoma cervix; locally advance disease. (FIGO stage IB2-IVA); age >18 but <70 years; ECOG performance 0-1-2; consenting for the study and Karnofsky performance status at least 40. Whereas patients with haematological, cardiac, renal or liver function abnormalities; hypersensitivity to Cisplatin with distant metastasis; prior Radiotherapy; Karnofsky performance status <40; Pregnant and lactating; with history of prior Chemotherapy (neoadjuvant), metastatic cancer and other synchronous malignancies were excluded from the study. A total of 80 patients met the inclusion criteria and thus were included in the study. After obtaining ethical clearance and consent from study participants, all the included patients were randomly divided into 2 groups using random number tables. Patients of group 1 received external beam radiotherapy (EBRT) along with weekly cisplatin 40 mg/m^2 followed by high-dose rate intracavitory brachytherapy (HDR ICBT) whereas patients of group 2 received EBRT with 3 weekly cisplatin 75 mg/m^2 followed by HDR ICBT.

Radiotherapy treatment protocol schedule in both arms included External Beam Radiotherapy delivered by Co60 teletherapy machine and HDR brachytherapy. Cases were treated by conventional radiotherapy schedule as follows: EBRT = 5000 cGy; HDR ICBT = 700 cGy X 3 # point A; Total Dose = 8000 cGy. EBRT was given 5 days a week with total duration of 35 days and after completion of EBRT 3 fraction of weekly ICRT was given. Portals for EBRT of pelvis: Parallel opposed (anterior posterior fields) /four field box technique. Radiation was delivered by conventional fractionation to a total dose of 46–50 Gy at the rate of 2 Gy per fraction, 1 fraction per day and 5 fractions per week in 23–25 fractions over a period of 5–6 weeks.

Cisplatin was given concurrently with EBRT once weekly (40 mg/m^2) for a total of five cycles in group 1 and once in 3 weeks (75 mg/m^2) for a total of two cycles in group B during the course of EBRT. Premedication in both the groups consists of Dexamethasone 8 mg IV, Ranitidine 50 mg IV and a 5HT3-receptor antagonist as antiemetic with hydration for two hours before and after chemotherapy with D5-NS at 150 cc/hr.

After chemotherapy, patients in both the groups were given 2 ampoules (300 mg) potassium chloride in 500 ml of 0.9% NS over 1 h followed by 2 ampoules of 50% w/v magnesium sulphate in 500 mL of 5% dextrose over 1 h. Also hydration was

maintained in post chemotherapy phase.

All patients were enquired about sociodemographic details and were subjected to thorough general examination. All patients were subjected to Complete blood examination, RBS, renal function test, liver function test, Chest x-ray (PA view), USG abdomen and pelvis. CT/MRI abdomen and pelvis was conducted when required.

Follow up :

All the patients were followed up at 6 weeks after completion of treatment and then they were followed up every 1 month for first 3 months, every 3 monthly for 9 months then for every 4 months for 2 years. Follow-up procedures include general, systemic and pelvic examination, palpation of inguinal and supraclavicular nodes. Imaging studies, such as radiograph, computed tomography, ultrasonography and bone scan were done when required.

Statistical analysis

The data was compiled using MsExcel and analysed using SPSS software version 20 (IBM SPSS Statistics, Somers NY, USA). Frequencies and percentages were calculated using grouped data. All the descriptive data was represented as mean ± SD. Student independent 't' test was used to compare the means of different continuous variables whereas Pearson's Chi-square test was applied to assess the association among different categorical variables. $P < 0.05$ was taken statistically significant.

RESULTS

The present study included a total of 80 patients diagnosed with locally advance cervical cancer. These patients were randomly allocated into 2 groups of 40 patients each. Patients in group 1 received Cisplatin concurrently with EBRT once weekly (40 mg/m2) for a total of five cycles whereas patients in group 2 received cisplatin once in 3 weeks (75 mg/m2) for a total of two cycles in group B during the course of EBRT.

Table 1- Distribution according to baseline characteristics

Sociodemographic variables		Group 1 (%)	Group 2 (%)	P value
Age group (years)	<40	9 (22.5)	6 (15)	0.78
	40-49	16 (40)	20 (50)	
	50-59	11 (27.5)	10 (25)	
	60-69	4 (10)	4 (10)	
Residence	Rural	25(62.5)	30 (75)	0.22
	Urban	15(37.5)	10 (25)	
ECOG status	0	0 (0)	0 (0)	0.61
	1	29 (72.5)	31 (77)	
	2	11(27.5)	9 (22.5)	
Socioeconomic status	Low	22(55)	24 (60)	0.65
	Middle	17 (42.5)	16 (40)	
	High	1(2.5)	0	
Stage	IIB	22 (55)	30 (75)	0.06
	IIIB	18 (46)	10 (25)	

Above table represents baseline characteristics of participants of two groups. The population in two groups was comparable in age composition, residence, ECOG status, socioeconomic status and stage of cervical cancer.

Table 2- Distribution according to chemotherapy in both the groups

Chemotherapy	Group 1 (%)	Group 2 (%)	P value
Dose per cycle (mg)	45.5	110.5	0.003
Cumulative dose (mg)	220	198	0.94

Patients in the group 1 received a mean dose of 45.5 mg per cycle, whereas patients in group 2 received mean dose of 110.5 mg per cycle and the observed difference was statistically highly significant ($p<0.01$). However, total cumulative dose in both the groups was statistically similar with a mean of 220 mg in group 1 as compared to 198 mg in group 2 ($p=0.94$).

Compliance of the treatment can be defined in terms of completeness of chemotherapy and radiotherapy within the prescribed time limits. For radiotherapy 56 days (8 weeks) was taken as standard and chemotherapy as per the schedule. In the group 1 the average time of completion of radiotherapy was 60 days, with maximum of 80 days and minimum of 50 days; 15 patients (37.5%) completed their radiotherapy within 56 days (8 weeks) of starting treatment, whereas 8 (20%) completed within 63 days (9 weeks) and 17 (42.5%) took more than 63 days (9 weeks) to complete the same. In the group 2, in which the average treatment time was 61 days, maximum time being 83 days and minimum 45 days; 12 patients (30%) completed within the prescribed time of 56 days (8 weeks), 15 (37.5%) within 9 week and 13 patients (32.5%) took more than 63 day (9 weeks) to complete the same.

About 34 patients (85%) and 37 (92.5%) in group 1 and group 2 respectively completed the full course of chemotherapy i.e. 5 cycles. 4 cycles were taken by 4 (10%) cases in group 1 and 2 (5%) patient in group 2. However, 2 (5%) and 1 (2.5%) patient respectively completed only3cycles of chemotherapy in group 1 and group 2.

Table 3: Acute toxicities in participants of 2 groups

Acute toxicities	Group	Grade 1	Grade 2	Grade 3	Grade 4	P value
Nausea	1	28 (70)	12 (30)	0 (0)	0 (0)	0.24
	2	23 (57.5)	14 (35)	3 (7.5)	0 (0)	
Vomiting	1	19 (47.5)	13 (32.5)	0 (0)	0 (0)	0.07
	2	13 (32.5)	22 (55)	0 (0)	0 (0)	
Diarrhea	1	22 (55)	7 (17.5)	2 (5)	0 (0)	0.2
	2	29 (72.5)	5 (12.5)	0 (0)	0 (0)	
Nephrotoxicity	1	3 (7.5)	0 (0)	0 (0)	0 (0)	0.06
	2	9 (22.5)	0 (0)	0 (0)	0 (0)	
Hyponatremia	1	4 (10)	0 (0)	0 (0)	0 (0)	0.13
	2	9 (22.5)	0 (0)	0 (0)	0 (0)	
Hypokalemia	1	4 (10)	0 (0)	0 (0)	0 (0)	1.0
	2	2 (5)	2 (5)	0 (0)	0 (0)	
Weight loss	1	13 (32.5)	3 (7.5)	0 (0)	0 (0)	0.37
	2	15 (37.5)	7 (17.5)	0 (0)	0 (0)	
Anemia	1	24 (60)	6 (15)	2 (5)	0 (0)	0.61
	2	25 (62.5)	11 (27.5)	0 (0)	0 (0)	
TLC	1	1 (2.5)	11 (27.5)	0 (0)	0 (0)	0.07
	2	6 (15)	9 (22.5)	0 (0)	0 (0)	
ANC	1	5 (12.5)	3 (7.5)	0 (0)	0 (0)	0.36
	2	1 (2.5)	4 (10)	0 (0)	0 (0)	

In present study, all patients were evaluated for toxicities based upon the guidelines of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.[13] No treatment related deaths were observed in present study. No statistically significant difference in occurrence of acute toxicities between the participants of two groups was observed ($p>0.05$).

Table 4- Distribution according to response to treatment in both the groups

Response to treatment	Group 1 (%)	Group 2 (%)	P value
Complete response	33 (82.5)	36 (90)	0.33
Partial response	7 (17.5)	4 (10)	

The patients were followed up at specified interval and final response was observed at 6 weeks after completion of therapy. Clinically, complete response was noted in 82.5% and 90% patients in group 1 and group 2 respectively. However the observed difference in response was not statistically significant ($p>0.05$).

DISCUSSION

Concurrent Chemoradiation with the help of cisplatin is a "standard of care" for women with locally advanced carcinoma cervix. This was in response to a National Cancer Institute Alert based results of five randomized trials stating "strong consideration should be given to the incorporation of chemotherapy and radiotherapy for the treatment of cervical cancer.[14] Weekly cisplatin based treatment regimen was recommended by National Comprehensive Cancer Network guidelines, based on the results of 5 randomized trials conducted during the 1990s.[4-9] Weekly smaller individual doses of cisplatin may lead to less CT-induced morbidity without compromising efficacy. However, three weekly cisplatin is popular in head-and-neck cancers. It is assumed that high dose three weekly cisplatin may also help in preventing distant metastasis by neutralising occult micrometastasis apart from radiosensitisation.[15] Ryu et al in their randomized trial using triweekly single CDDP chemotherapy concurrent with RT documented better 5-year survival and lower incidence of hematological toxicity compared with the conventional weekly CDDP in patients with LACC.[11]

In the present study, 85% and 92.5% in group 1 and group 2 respectively completed the full course of chemotherapy and the most common reason for incomplete treatment was haematologic toxicity. These findings were similar to study conducted by Anusha et al.[16] However in another similar study by Ryu et al, the two regimens were tolerated very well, with 86.3% and 92.5% completion of scheduled CT cycles for the weekly and triweekly arms, respectively.[11]

The present study observed neutropenia and GI toxicities as the most common acute toxicities, however, no statistically significant difference was observed for any toxicities between the participants of 2 groups ($p>0.05$). Nauseas was reported by all the patients in both the groups. These findings were supported by Anusha et al and Ryu et al.[16,11] However, Lee et al documented contrasting results in which tri weekly cisplatin was associated with higher incidence of leucopenia (96%) as compared to weekly cisplatin group (85%).[12] Prolonged treatment time had an adverse effect on outcome because of accelerated repopulation of tumor and thus any delays must be avoided.[16]

At 6 weeks, following treatment, complete response was observed in 82.5% and 90% patients in group 1 and group 2 respectively in present study. These finding were similar to the findings reported by Anusha et al in which complete response was seen in 17 (85%) patients of arm A, 19 (95%) patients of arm B.[16] The reference study and present study observed no statistically significant difference in treatment response between two groups. However, Ryu et al documented better survival rate in patients in 88.7% cases with tri weekly cisplatin at 5 years versus 66.7% for the weekly cisplatin arm.[11]

CONCLUSION-

The present study documented similar response and toxicity profile of both the regimens and thus concurrent weekly or 3 weekly cisplatin along with radiotherapy can be used with equal effectiveness in the treatment of cervical cancer. Long term follow up of these patients is needed to reach any definite conclusion regarding its effect on overall survival.

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