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A PROSPECTIVE STUDY ON DAILY LOW DOSE CISPLATIN CONCURRENT WITH INTENSITY MODULATED RADIOTHERAPY IN LOCALLY ADVANCED CARCINOMA CERVIX

Oncology

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ABSTRACT

Treatment of locally advanced cervical cancer evolved from EBRT alone to EBRT plus ICRT to EBRT with concurrent chemotherapy plus ICRT. Concurrent cisplatin therapy is usually administered on a weekly or three weekly basis. The doses of Cisplatin used in the weekly or three weekly regimen may not be tolerated well by all patients, resulting to fewer patients being able to receive the total planned effective dose of concurrent chemotherapy. Experimental data suggest that antitumor activity of cisplatin may be greater if administered by continuous infusion. Preliminary studies have also shown that low dose, daily Cisplatin with radiotherapy may be better tolerated along with similar response rates, especially in older age patients. **Results:** Overall 96.8 % (30 out of 31) of the patients had complete response and 3.2% (1 out of 31) patients had partial response. Almost all (except one) the patients in the study received a cumulative dose of 200 mg/m2 of concurrent Cisplatin. Acute grade 3 toxicities were observed mostly in the form of diarrhoea and skin toxicity. Grade 3 diarrhoea occurred in 14 patients (45.2%). Incidence of acute grade 3 skin reaction was seen in 2 patients (6.5%), whereas the incidence of acute grade 3 haematological toxicity , genitourinary toxicity and grade 3 nausea and vomiting was nil. **Conclusions:** A daily low dose cisplatin prior to radiotherapy might lead to an increased radiosensitization as well as better tolerance than other regimens.

KEYWORDS

cervical cancer, cisplatin, daily low dose chemotherapy, IMRT

INTRODUCTION

According to Global cancer statistics 2018: GLOBOCAN, In 2018, there were an estimated 569 847 new cases and 311 365 deaths due to cervical cancer worldwide .85% of the cases occur in developing countries [1-5]. Infact, it is the leading cause of cancer related deaths among women in developing countries [1].

Treatment of cervical cancer depends on the stage of the disease, patient's general health and her desire to have children. The usual treatment protocol of early stage cervical cancer is either surgery or radiotherapy (RT). Radiation therapy is the standard of treatment for locally advanced cervical cancer (for stages IB2 to IVA)[6].

The treatment of locally advanced cervical cancer evolved from EBRT alone to EBRT plus brachytherapy (ICRT) to EBRT with concurrent chemotherapy plus ICRT[7-13].

Despite intensification of treatment the prognosis is poorer as the stage of the disease advances[14].

Several randomized controlled trials[15-18] have shown that cisplatin based concurrent chemoradiotherapy (CCRT) improves the prognosis of advanced cervical cancer. The method of administration of cisplatin varies from study to study and the optimum dose and method remains to be established. Most studies showed survival improvement with CCRT administered with a weekly 40 mg/m2 compared to tri-weekly 75 mg/ m2 dosage.

Cisplatin when administered prior to radiotherapy, lead to an increase in the slope of the radiation dose-response curve. Experimental data also suggest that antitumor activity of cisplatin may be greater if administered by continuous infusion[19].

A daily low dose cisplatin prior to radiotherapy might lead to an increased radiosensitization as well as better tolerance than other regimens.

IMRT is increasingly being used in the treatment of cervical cancer. IMRT can potentially improve the therapeutic ratio because of its ability to deliver higher dose to cancer targets while sparing the nearby healthy tissues[20-22].

A randomized study conducted by the European Organization for Research and Treatment of Cancer (EORTC) for advanced lung cancer on the efficacies of daily CCRT in lung cancer showed that it possibly had a better local control rate with fewer adverse effects compared to weekly CCRT[23]. But there are very few studies on the feasibility of daily CCRT for cervical cancer with low dose cisplatin for patients with locally advanced cervical cancer[24-28].

AIMS AND OBJECTIVES:

- To assess the response of treatment to daily low-dose cisplatin concurrent with IMRT in cervical cancer.
- To assess the acute and late toxicity of treatment.

METHODOLOGY:

Patients were selected for the study after discussion in the multidisciplinary tumor board of the institute. All the eligible patients were informed about the extent of their disease, treatment available to them along with possible complications of the treatment in terms and language that they understand.

After taking proper consent, patients were taken up for the study. The study commenced after approval of the ethical committee. The number of subjects for this study was 31 with power 91%.

Statistical Analysis was performed with the help of Epi Info (TM) 7.2.2.2. EPI INFO is a trademark of the Centre for Disease Control and Prevention (CDC).

Inclusion Criteria :

Women in the age group of 20 to 75
FIGO stage IB2 to IIIB
Histologically proven cervical cancers
Patients who have not received any previous treatment for cervical cancer
Liver function test and renal function tests within normal limits.

Haemoglobin more than 10 g%, total white blood cell count within 4000 to 11000, platelet count more than 1 lakh.

Patients' Eastern Cooperative Oncology Group (ECOG) score 0 to 2 before initiation of treatment.

Patient's consenting to participate in the study.

Patient's with no other primary malignancy.

After proper history taking patients were clinically examined .Patients were then investigated with baseline CBC (complete blood count), KFT (kidney function test), LFT (Liver function test), X-ray chest and USG (ultrasonography) of abdomen-pelvis.

Treatment Methods:

All the selected patients were taken for CT simulation (with i.v. and oral contrast) following a bladder protocol.

The image-data thus generated was transferred to Monaco treatment planning system (TPS) for delineation of contour and different target volumes (GTV, CTV and PTV) according to the ICRU-50,62&83 report[29].Organs at risk (OARs) were delineated properly and the dose constraints were as per the standard guidelines (QUANTEC)[30].

The radiotherapy equipment used in this study is a dual-energy (6MV & 15MV) Linear Accelerator (Elekta Synergy ®) owned by the institute.

Inverse treatment planning was performed using monte-carlo algorithm, CMS MONACO treatment planning system (V.3.30.01, ELEKTA).

Particular plan was approved if the prescribed dose covered 95% of PTV with maximum target dose less than 108%. Normal tissue dose volume was maintained within 5% of the constraints prescribed. Dose volume histograms as well as every single slices were evaluated carefully before final approval of plan.

Approved plans were sent to Mosaiq (record and verify system for treatment delivery). VMAT technique was used to deliver radiotherapy on a linear accelerator (ELEKTA SYNERGY) with 80-leaf multi-leaf collimators.

Patients received the daily radiotherapy fractions following the same bladder protocol.

Chemotherapy:
Daily low dose cisplatin- 8mg/m^{2}was administered prior to EBRT on day 1 to day 5 of every week.Patients received 8 mg of ondansetron intravenously one hour before administering cisplatin to prevent emesis.Cisplatin was administered intravenously for 30 minutes and was completed 1 hour before EBRT. The daily dose of cisplatin was reconstituted in 100 ml normal saline.

Brachytherapy:
In this study, EBRT was given upto a dose of 50Gy in 25 fractions (2 Gy per fraction) for 5 weeks to whole pelvis using IMRT in linear accelerator (6 MV).

Intracavitary brachytherapy (ICBT) was started after completion of four weeks of EBRT. HDR-ICBT was performed weekly with a prescribed dose to point A as 6 Gy per fraction for 4 fractions.

Brachytherapy Machine:
Microselectron HDR V3 integrated brachytherapy unit.

The procedures were done under sedation.

After proper application digital imaging (using 2-D X-ray C-arm) were done to confirm application accuracy.

Dose to bladder and rectum estimated as per International Commission on Radiation Units and Measurements (ICRU) definition (ICRU-38) and proceeded with the treatment delivery only when the organ at risk (OAR) doses were considered safe.

During the course of treatment each patient was monitored for any acute toxicity using CTCAE criteria version 4.2. Radiotherapy was stopped with the appearance of grade 3 or higher acute toxicity, and was resumed after recovery to grade 2.

Follow Up:
All patients were reviewed after one month of completion of therapy to assess the response (with the help of RECIST criteria [31]) and late complications (using CTCAE criteria) of the therapy if any. During the follow-up, recurrence was to be confirmed by clinical and radiologic study. Hematological toxicity and non-hematological toxicities (weight loss, diarrhea, abdominal pain, nausea and vomiting) were classified by the National Cancer Institute - Common Toxicity Criteria (CTCAE).

RESULTS:
The mean age (mean ± s.d.) of the patients was 55.71±8.05years with range 36 – 70years and the median age was 56 years. As per HPE all the patients were with SCC (100.0%).

Table 1. Patient characteristics

Characteristic	Value (median)
Age (yr)*	56 (36-70)
BMI	22.6 (18.8-32.8)
BSA	1.4 (1.3-1.7)
FIGO stage	
IB2	0
IIA	0
IIB	15
IIIA	0
IIIB	16
IVA	0
Histology	
Squamous cell carcinoma	31
Well differentiated	5
Moderately differentiated	18
Poorly differentiated	8
Adenocarcinoma	0
Others	0
ECOG 0	22
ECOG 1	9
Duration of follow-up (months)* 5(1-12) 17(12-24)	

- Mean ICRT dose was 6 GY per fraction.
- Mean duration of completion of ICRT was 31 days, ranging from 28 to 36 days.

EBRT
- Mean EBRT dose was 49.8 GY, ranging from 44 GY to 50 GY.
- Mean duration of completion of EBRT was 39 days, ranging from 33 to 50 days
- The mean duration of overall treatment (mean ± s.d.) of the patients was 9.32±0.58 weeks with range from 8.14 to 10.29 weeks and the median duration was 9.29 weeks.

Chemotherapy
- Mean dose of concurrent cisplatin was 10.5 mg, ranging from 10 to 12 mg

Table 2. Characteristics of chemoradiotherapy

Characteristic	Value (median)
Duration of External beam radiotherapy (day)	38 (33-50)
External-beam radiotherapy dose (Gy)	50 (44-50)
EBRT dose per fraction(Gy)	2
Brachytherapy dose, EQD2 (Gy)	32 (29.7-32)
Brachytherapy dose per fraction	6(6-7)
Brachytherapy no of fractions	4(3-4)
Total treatment duration(weeks)	9(8-10)
Daily dose of cisplatin (mg/day)	10 (10-12))
Total cumulative dose of cisplatin (mg)	250 (220-250)
Interruption of therapy	
No	23
Yes	8
Duration of interruption(days)	1-4
Cause of Interruption	
Diarrhea	7
Skin reaction	1

Table 3. Treatment Response

Variable	No. (%)
Local response	
CR	30 (96.8)
PR	1(3.2)
Recurrence	1 (3.2)
Site of recurrence	
Pelvic only	0
Para aortic	1

Follow Up:
Mean duration of follow up was 16.6 months, ranging from 12 to 24 months.

DISCUSSION:
In this study 31 cervical cancer patients were treated with radiotherapy (50 Gy in 25 fractions) plus concurrent low dose daily cisplatin (8 mg/m2) and HDR intra-cavitary brachytherapy (6 Gy/fraction x 4 fractions) between November 2017 to june 2020. The mean duration of follow up was 16.6 months.

Thirty (30) patients completed the full course of treatment except one patient who could not receive EBRT beyond 22 fractions due to severe diarrhoea and skin reaction. Overall 96.8 % (30 out of 31) of the patients had complete response and 3.2% (1 out of 31) patients had partial response.

Till last contact, 28 patients out of 31 patients, who showed complete response to treatment were alive and disease free. One patient who had partial response was alive with residual disease. She is under close follow up and evaluation for further line of management.

All the acute toxicities related to IMRT plus concurrent chemotherapy and ICRT were within expected limits and overall the whole course of treatment was tolerated well by most of the patients. Acute grade 3 toxicities were observed mostly in the form of diarrhoea and skin toxicity. Grade 3 diarrhoea occurred in 14 patients (45.2%). Incidence of acute grade 3 skin reaction was seen in 2 patients (6.5%), whereas the incidence of acute grade 3 haematological toxicity , genitourinary toxicity and grade 3 nausea and vomiting was minimal / nil.

Eight (8) patients (25.8%) out of the 31needed treatment breaks but among those only 5 patients (16.1%) suffered treatment interruption of 3 or more days. Diarrhoea was the most common cause of treatment interruption.

Till the date of last follow-up most common late toxicities were those of genitourinary and gastrointestinal. Incidence of grade 3 or grade 4 late toxicities were not observed till date in any of the patients. Four (4) patients suffered grade 2 late genitourinary toxicity and two (2) patients showed the features of grade 2 late bowel toxicity.

Even after treating with concurrent chemoradiotherapy the incidence of acute haematological toxicities were much less as there was no acute grade 3 haematological toxicity. Only 38.7% and 6.5 % grade 2 anaemia and leucopenia respectively were observed. This low incidence of haematological toxicity is most likely due to a reduction in dose to bone marrow achieved with IMRT. In Gynecologic Oncology Group (GOG) Trial 123 (369 cases) with a 40 mg/m2 weekly cisplatin, grade 3 and 4 hematological toxicities were observed in 18% and 3% of patients, respectively.

The potential for normal-tissue sparing and achieving good target coverage are the motivations behind the move towards IMRT for cervical cancer. But the large PTV margins required to compensate for organ motion are also likely to result in increased doses being delivered to surrounding normal tissues, thereby increasing toxicity.

The review of literature revealed that the local control and acute and late toxicity results of our study are comparable with study by KimioUshijima, et al[25], where the overall response rate was 94.1% with grade 3 or 4 neutropenia observed in 37.3% of the patients. Our study had a 96.8% complete response rate and none of the patients developed grade 3 or higher grade of neutropenia.

In our study also all except one patient completed the full course of treatment and no treatment interruption were due to haematological toxicities. Thus almost all (except one) the patients in the study received a cumulative dose of 200 mg/m^2 of concurrent cisplatin. In GOG Trial 120 (575 cases) with 40 mg/m2 of weekly cisplatin, only 49.4% of patients could be administered 6 or more cycles of Cisplatin.

Using IMRT technique, radiotherapy was much better tolerated in the study population with not much treatment interruption and significantly low toxicity profile compared to conventional RT used in most of the previous similar studies.

There were no CTCAE grade 4 acute toxicities in our study cases. A daily low dose cisplatin prior to radiotherapy might lead to an increased radiosensitization as well as better tolerance than other regimens. Moreover a daily low dose of cisplatin can be administered safely even in elderly patients where higher dosage is limited by age-associated decline in renal mass and glomerular filtration rate. Daily low dose cisplatin offers ease of administration in outpatient clinic (obviating the need of hydration, diuresis and hospitalization).

Preliminary results from similar studies of early response of bulky cervical tumor treated with radiation therapy and daily low dose cisplatin were also encouraging [18]. In this study we evaluated the possible toxicities and response of the tumor to daily low dose (8mg/m^2) cisplatin as a radiosensitizer in patients with locally advanced cervical cancer in a tertiary care setting of eastern India.

IMRT is increasingly being used in the treatment of cervical cancer. IMRT can potentially improve the therapeutic ratio because of its ability to deliver higher dose to cancer targets while sparing the nearby healthy tissues.

Thus this study is one of the first to evaluate the feasibility of daily low dose concurrent cisplatin with IMRT in carcinoma of cervix in Indian population.

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