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A Study on the Response of Concurrent Chemo-radiation with Gemcitabin followed by Intracavitary Radiotherapy in Patient with Locally Advanced Cervical Carcinoma

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Abstract **Original Research Article**

Introduction*: C**ommonest threatening cancer in our Asian round is Cervical cancer. Currently, platinum based concurrent chemo-radiation therapy is the standard of care for locally advanced cervical cancer but treatment results are disappointing, particularly for women with bulky tumor. To improve this result, several non-platinum based agents with concurrent chemo-radiation have been evolved. ***Objective*:** To observe the response and toxicity of concurrent chemo-radiation with Gemcitabine including intracavitary radiotherapy in patients with locally advanced cervical carcinoma. ***Material and Methods: This was a quasi-experimental study, where 33 patients with untreated invasive squamous cell carcinoma of the cervix of stage IIB to stage IVA were enrolled in the study from the Radiation Oncology Department of Rajshahi Medical College Hospital from April 2019 to March 2020. Duration of the study was 2 years. All patients received 150 mg/m² of Gemcitabine weekly along with external beam radiation therapy (EBRT). EBRT dose was 50 Gy in 25 daily fractions followed by intracavitary radiotherapy (ICRT) of 21 Gy in 3 fractions. ***Results*:** The mean age was 45.4 years. Most of the patients were in stage IIB group (59.1% patients) and most of them were moderately differentiated (62.1% patients). After 3 months of treatment, the complete response was found in 81.8% patients and partial response was seen in 12.1% patients and progressive disease was found in 6.1% patients. The grade 2 and 3 haematological toxicity was higher. The grade 2 and 3 anaemia was seen in 60.6% and 24.2% patients, neutropenia was observed in 24.2% and 6.1% patients respectively. The grade 2 diarrhoea (42.4%), proctitis (36.4%) and skin toxicity (45.5%) were more common. The grade 1 renal toxicity was observed in 3% patients and grade 2 cystitis was found in 9.1% patients. ***Conclusion*:** Concurrent chemo-radiation with Gemcitabine can be used as an alternative to Cisplatin, when cisplatin is contraindicated. However further large randomized study is needed to reach any form of conclusion.

Keywords: Locally advanced cervical cancer, concurrent chemo-radiation, Gemcitabine.

INTRODUCTION

The fourth most common malignancy among women with both incidence (6.6%) and mortality (7.5%) is cervical cancer. WHO recommended it in 12th September 2018. Approximately 90% of deaths from cervical cancer occurred in low and middle income countries. It is evident that, in Asian region, half of the of all cases and deaths from the disease worldwide, with South Central and Southeast Asia having the highest incidence and mortality rates. According to the report of 2018, American cancer society of clinical oncology revealed that the 5-year survival rate for all women with cervical cancer is about 67%. The type of treatment for cervical cancer depends on the stage of the disease and different treatment groups with curative intent have been established. According to the classification of the International Federation of Gynecology and Obstetrics (FIGO cancer report, 2018) stages between IIB and IVA are defined as locally advanced cervical cancer (LACC), which includes tumor with parametrial invasion (IIB), involve the lower third of the vagina but not extending to

the pelvic wall (IIIA) or extending to the pelvic sidewall and/or involving the lower third of the vagina and/or causing hydronephrosis or nonfunctioning kidney (IIIB), invasion to the mucosa of the bladder or rectum and/or extending beyond the true pelvis (IVA). For locally advanced cervical cancer, concurrent chemoradiation is the treatment of choice in many countries [1]. There was a meta-analysis whereas, 18 randomized trial done by patients, revealed chemo-radiation improves local & distant recurrence & there is an evidence of disease free survival [2]. Many studies showed that the standard of care for locally advanced cervical cancer is concurrent chemoradiation (CCRT) with cisplatin followed by brachytherapy [3-5]. Platinum based chemotherapy improves progression free survival& declines 30-50% risk of death in locally advanced cervical cancer. A recent meta-analysis of 8 randomized trial support this claim [6].

In the recent years, from the introduction of chemo-radiation (CRT), there have been no further advances in the management of locally advanced cervical cancer. Although most of the trial showed cisplatin is the most efficacious but the jury is still out there searching for the best drug available in concurrent setting. Some studies showed better response (CR>80%) in combination of platinum with non- platinum based chemotherapy but toxicity rates were higher [7-9]. To enhance the survival of overall disease, there is a need to explore the use of alternative chemotherapeutic agents. A variety of agents such as carboplatin, paclitaxel, 5-FU have been studied with good result in cervical carcinoma.

Gemcitabine is a cell cycle specific cytotoxic agent & a novel deoxycytidine analogue [10]. It acts as a radiosensitizer at low doses & also shows synergestic effect with cisplatin [11]. Gemcitabine has been used in cervical cancer with good result both as a single agent & in combination with cisplatin concurrent with radiotherapy [12, 13].

METHODS AND MATERIALS

This prospective quasi-experimental study was conducted in the Department of Radiotherapy, Rajshahi Medical College and Hospital, Rajshahi from June 2018 to September 2020.

Eligibility Criteria:

Newly diagnosed 33 patients with histopathologically confirmed locally advanced squamous cell carcinoma of cervix, with FIGO stage IIB to IVA and no evidence of distant metastasis were enrolled in this study. ECOG performance score was upto 2 and age between 18 years and 60 years. Patients were excluded if there was evidence of uncontrolled infection, patients with double primaries, pregnant or lactating woman. Written informed consent was obtained from the patients prior to participation in the study and ethical clearance was given by local ethics committees.

Treatment Schedule

Radiotherapy

All patients were irradiated by external beam radiotherapy to the pelvis using cobalt-60 machine with a total dose of 50 Gy given in 25 fractions of 2 Gy per fraction, 5 fractions per week starting 1st day of the first chemotherapy. Anterior and posterior field was used where superior border was at L5-S1 junction, inferiorly at the bottom of the obturator foraman or the lower extension of the disease and laterally 2 cm beyond the lateral margins of the bony pelvic wall.

Intracavitary Radiotherapy

All the patients were treated with high dose rate intracavitary brachytherapy using after-loading cobalt-60 sources (within 1 week of completion of treatment with EBRT). A dose of 7 Gy per fraction, total 21 Gy in 3 fractions over 3 weeks were given to the point A. Bladder and rectal dose were limited to 80% prescribed dose as per ICRU recommendations.

Chemotherapy

All patients who are included in concurrent chemo-radiation, with weekly Gemcitabine at a dose of 150 mg/m^2. It was administered 2 hours before radiotherapy and after giving premedication. Gemcitabine was diluted in 250 ml normal saline and infused over 30 minutes. No pre or post-hydration was given.

Patient Assessment

During concurrent chemo-radiation therapy, patient was assessed every week during therapy. Symptomatic response and acute toxicities were assessed in every week with physical examination. Tumor response was evaluated according to RECIST criteria. Toxicity was observed according to RTOG cooperative group common toxicity criteria and common terminology criteria for adverse effects (CTCAE) version 5.0 (2018). After treatment, the first follow-up at 6th week and second follow-up at 12th week was recommended for the response. Follow up examination includes history taking, physical examination, radio-logical and laboratory tests as needed.

Statistical Analysis

Data analysis was done according to the objectives of the study by using the SPSS (Statistical Package for Social Science) software program for windows, version 20.0 available in the institute.

RESULTS

A total 33 patients were analyzed in this study. Detailed of patient's characteristics are shown in Table 1. The mean age was 45.36 (SD: 9.270, range: 25-60) years. Most of the patients (81.8%) came from lower economic class, 15.2% came from middle class and 3% belong to upper class. Among them most of the patients (54.5%) were illiterate followed by 36.4% patients passed primary. Most of the patients were in stage IIB

group (60.6% patients). 6.1% patients with stage IIIA, 30.3% patients with stage IIIB and 3% patients with stage IVA, were enrolled in this study. Most of them (63.6%) were moderately differentiated, 15.2% were well differentiated and 21.2% poorly differentiated. According to ECOG performance status 75.8% patients were in PS 0, 1 group and 24.2% patients were in PS 2 group. Early onset of sexual exposure was the most important causative risk factor contributing cervical carcinoma (78.8% patients) [Figure 1]. Other factors included taking of OCP more than 5 years (75.6%), unhealthy personal hygiene (72.7%) and multi-parity (36.4%). Clinical feature was demonstrated in Figure 2. Most common symptom was vaginal discharge (90.9%). Other frequent symptoms were post coital bleeding (48.5%), abnormal vaginal bleeding (48.5%), and pain in the pelvis (48.5%).

After completion of CCRT 20 patients (60.6%) showed complete response and 12 patients (36.4%) had partial response and 1 patient (3%) had stable disease. After completion of intracavitary radiotherapy (ICRT), 22 patients (66.7%) had complete response while 11 patients (33.3%) had partial response. After 6 weeks of completion of treatment 25 patients (75.8%) showed complete response while 7 patients (21.2%) had partial response, 1 patient (3%) had stable disease and 1 patient (3%) had progressive disease After 3 months of treatment, the complete response was found in 81.8% and Partial response was seen in 12.1% patients and progressive disease was found in 2 (6.1%) patients. Treatment response is listed in Table 2.

The grade 2 and 3 haematological toxicity was higher. The grade 2 and 3 anaemia was seen in 60.6% and 24.2% patients respectively. The grade 2 and 3 neutropenia was observed in 24.2% and 6.1% patients respectively. The grade 1 thrombocytopenia was seen in 24.2% patients. The grade 2 and 3 vomiting was observed in 24.2% and 6.1% patients while the grade 2 and 3 diarrhoea was observed in 42.4% and 15.2% patients respectively. Skin toxicity, cystitis and proctitis were observed in all patients. The grade 2 and 3 skin toxicity were observed in 45.5% and 15.1% patients respectively. 36.4% patients showed grade 2 proctitis while 9.1% patients showed grade 3 toxicity. The grade 1 cystitis was observed in 90.9% patients while 9.1% patients showed grade 2 cystitis. Vaginal mucositis was observed in 23 patients (45.5% patients showed grade 1 while 24.2% patients showed grade 2 toxicity). The grade 1 renal toxicity was observed in 3% patients (Table 3).

Table 1: Patient's baseline characteristics

Baseline characteristics		**N=33**	**%**
Age (years)	Mean ± SD	45.36 ± 9.270	
Education	Illiterate	18	54.6%
	Primary	12	36.4%
	SSC	3	9.1%
Economic status	Lower class	27	81.8%
	Middle class	5	15.2%
	Upper class	1	3.0%
ECOG performance status	PS=0,1	25	75.8%
	PS=2	8	24.2%
Histology grading	Well differentiated (10)	5	15.2%
	Moderately differentiated (41)	21	63.6%
	Poorly differentiated (15)	7	21.2%
Stage	Stage IIB	20	60.6%
	Stage IIIA	2	6.1%
	Stage IIIB	10	30.3%
	Stage IVA	1	3%

Table 2: Clinical Response at the end of treatment

Response	**CR**	**PR**	**SD**	**PD**
Response after EBRT	60.6% (20)	36.4% (12)	3% (1)	0
Response after ICRT	66.7% (22)	33.3% (11)	0	0
Response after 1st follow up	75.6% (25)	21.2% (7)	3% (1)	0
Response after 2nd follow up	81.8% (27)	12.1% (4)	0	6.1% (2)

***EBRT=External beam radiotherapy; ICRT=Intracavitary radiotherapy; CR=Complete response; PR=Partial response; SD=Stable disease; PD=Progressive disease*

Table 3: Acute Toxicity of Chemoradiation with Gemcitabine

Toxicity	Grade I	Grade II	Grade III
Haematological toxicity			
Anaemia	27.3% (9)	60.6% (20)	12.1% (4)
Neutropenia	48.5% (16)	24.2% (8)	6.1% (2)
Thrombocytopenia	24.2% (8)	0	0
Nonhaematological toxicity			
Vomiting	39.4% (13)	24.2% (8)	6.1% (2)
Diarrhoea	27.2% (9)	42.4% (14)	15.2% (5)
Proctitis	54.5% (18)	36.4% (12)	9.1% (3)
Cystitis	90.9% (30)	90.9% (3)	0
Renal toxicity	3% (1)	0	0
Skin toxicity	39.4% (13)	45.5% (15)	15.1% (5)
Vaginal mucositis	45.5% (15)	24.2% (8)	0

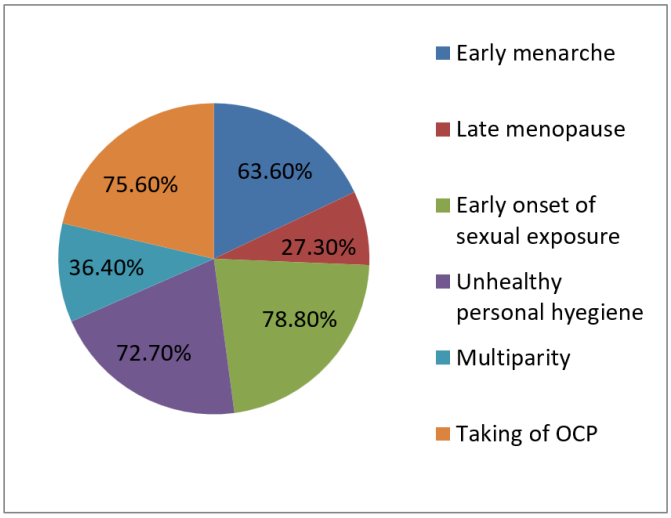

Figure 1: Risk factors

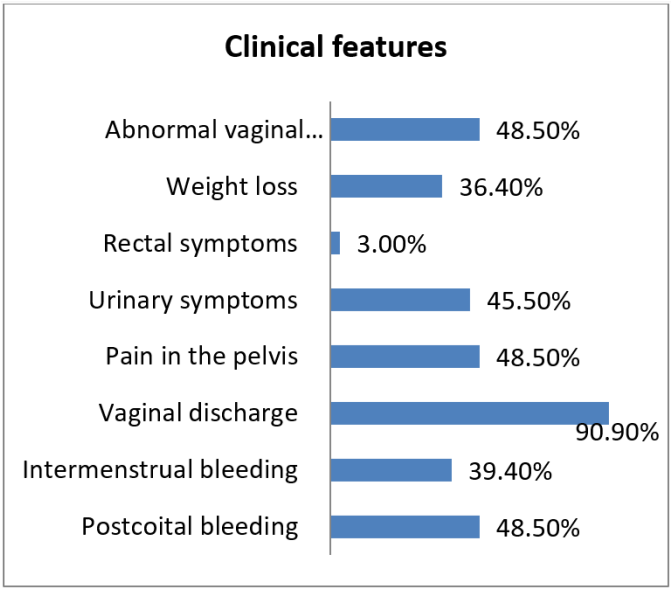

Figure 2: Clinical features

DISCUSSION

Cervical cancer is one of the commonest cancers in gynae is cervical cancer over the world. Cervical cancer treatment is a bit of challenging in a developing country like Bangladesh as most of the cases presented with advanced stage due to lack of screening and early detection programs. Previous clinical studies showed that the standard of care for locally advanced

cervical cancer is concurrent chemoradiation (CCRT) with cisplatin followed by brachytherapy [3, 4]. Despite of using concurrent cisplatin along with radiation loco-regional failure rate is going to an alarming rate. For the improvement of loco-regional failure rate other approaches were analysed with different regimens. Gemcitabine has a promising characteristics for the effect in clinical phase II trials [13].

In this study, starting during the period of June 2018 to August 2020 aimed to see the treatment outcome of concurrent chemoradiation with weekly gemcitabine in locally advanced cervical carcinoma. During this period patients with locally advanced cervical carcinoma were assessed for eligibility and ultimately 33 patients were included in the study after meeting inclusion criteria and giving written consent.

The mean age was 45.5 (SD ± 9.270) years (range: 25-60 years) and majority of the patients were in between middle of age group (72.7%). This observation correlates with SEER 2016 and CDC statistics 2017. Majority of the patients were from low socioeconomic condition (81.8%) and most of them were illiterate (54.5%). Early onset of sexual exposure was the most important causative exaggerating factor for the occurrence cervical carcinoma (78.8%) as most of the patients got married before 16 years of age. Other factor includes taking of OCP (75.8%), early menarche (63.6%), unhealthy personal hygiene (72.7%) and multiparity (36.4%). According to the study of Louie *et al.*, (2009), early marriage, low socio-economic condition, illiteracy, early age of intercourse were most common risk factors for developing carcinoma cervix and this study complies all of these observations. Here most of the patients were in stage IIB (60.6%) and majority of them were moderately differentiated (63.6%). This observation correlates with the study conducted by Thakur *et al.*, (2018). among all the common presenting symptoms, the most common symptom was vaginal discharge (90.9%). Other symptoms were post coital bleeding, abnormal per-vaginal bleeding and pain in the pelvis. After completion of treatment, control of per vaginal bleeding was observed in all patients, but some of the patients had persistent per vaginal watery discharge though the amount of discharge was reduced. Some of the patients had pelvic pain, dysuria, anaemia, loss of appetite and rectal discomfort even after completion of the treatment.

Response evaluation was done after completion of CCRT and brachy-therapy and according to the follow up schedule, it was set earlier. Before 36.4% had partial response and 3% had stable disease, CCRT 60.6% patients showed complete response After completion of intracavitary radiotherapy (ICRT), 66.7% patients had complete response while 33.3% patients had partial response. At first follow-up, 6 weeks after completion of treatment 75.8% patients showed complete response while 21.2% had partial response, 3% had stable disease and 3% had progressive disease. After 3 months of treatment, the complete response was found in 81.8% and Partial response was seen in 12.1% patients. This result correlates with the study of Verma *et al.*, (2009), where in gemcitabine arm complete response was 70%. Chufal *et al.*, (2007) conducted a study (gemcitabine dose 300 mg/m^2) where after completion of EBRT, complete response was 81.8% in gemcitabine group and 56.2% in cisplatin group and haematological and gastrointestinal toxicity was significantly higher in gemcitabine group. In the study of Cetina *et al.*, (2004), complete response was 89% where gemcitabine dose was 300 mg/m^2. In case of combination chemotherapy of gemcitabine and cisplatin concomitant with EBRT response rate is higher with increase rate of adverse effect (Zarba *et al.*, 2003; Hashemi *et al.*, 2013). In the study of Umanzor *et al.*, (2006) combination chemotherapy used with radiotherapy, complete response was 90% but gastrointestinal toxicity was higher. During radiotherapy patients were assessed weekly for toxicity. Most common acute toxicities were gastrointestinal (diarrhea, proctitis) and haematological (Anaemia, Neutropenia, Thrombocytopenia) toxicities. There was no treatment-related mortality identified in the present study. The grade 2 and 3 anaemia and neutropenia were higher (60.6% and 24.2% anaemia; 24.2% and 6.1% neutropenia respectively). The grade 2 vomiting and diarrhoea was also higher (24.2% and 42.4% respectively). Skin toxicity, cystitis and proctitis were observed in all patients but grade 2 skin toxicity and proctitis were higher (45.5% and 36.4% respectively. Grade 1 renal toxicity was found in 3% patients. In the study of kundu *et al.*, (2008) the grade 2-3 dermatitis & diarrhoea was higher in gemcitabine arm, which was similar with this study. In the year of 2004 cetina *et al.*, CCRT with weekly gemcitabine was given in patients with renal dysfunction and reported improvement of renal function with satisfactory response rate (89%).

CONCLUSION

So in conclusion it can be said that gemcitabine can be given as an alternative to cisplatin in patients with impaired renal functions. However, one should be aware that CCRT with gemcitabine is associated with considerable acute toxicity including hematological and gastrointestinal toxicity which is manageable.

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