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Comparison between The Efficacy of Concurrent Chemo-Radiation with Gemcitabine Followed by Intracavitary Radiotherapy in Patients with Locally Advanced Cervical Carcinoma

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ABSTRACT

Introduction: Commonest 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 tumors. To improve this result, several non-platinum-based agents with concurrent chemo-radiation have been evolved.

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 patient age was 45.4 years. Most patients were in stage IIB (59.1%) with moderately differentiated tumors (62.1%). After three months of treatment, 81.8% showed complete response, 12.1% partial response, and 6.1% disease progression. Grade 2 and 3 hematological toxicities were common, including anemia (60.6% grade 2; 24.2% grade 3) and neutropenia (24.2% grade 2; 6.1% grade 3). Other side effects included diarrhea (42.4%), proctitis (36.4%), skin toxicity (45.5%), mild renal toxicity (3%), and grade 2 cystitis (9.1%).

Conclusion: Gemcitabine-based concurrent chemo-radiation is a potential alternative for patients contraindicated for Cisplatin. However, larger randomized studies are needed to confirm its safety and efficacy.

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INTRODUCTION

The fourth most common malignancy among women with both incidence (6.6%) and mortality (7.5%) is cervical cancer. WHO recommended it on 12th September 2018. Approximately 90% of deaths from cervical cancer occured 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 tumors with parametrial invasion (IIB), involves 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 trials were done by patients, revealed chemo-radiation improves local and distant recurrence and 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 and declines 30-50% risk of death in locally advanced cervical cancer. A recent meta-analysis of 8 randomized trials supports this claim [6].

In 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 a 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, and 5-FU have been studied with good results in cervical carcinoma.

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

MATERIAL AND METHODS

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 the cervix, with FIGO stage IIB to IVA and no evidence of distant metastasis were enrolled in this study. ECOG's performance score was up to 2 and age between 18 years and 60 years. Patients were excluded if there was evidence of uncontrolled infection, patients with double primaries, and pregnant or lactating women. 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 a 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. The anterior and posterior field was used where a 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 of 21 Gy in 3 fractions over 3 weeks was given to point A. Bladder and rectal doses 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 of normal saline and infused over 30 minutes. No pre or post-hydration was given.

Patient Assessment

During concurrent chemo-radiation therapy, the patient was assessed every week during therapy. Symptomatic response and acute toxicities were assessed in every week with a 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 the second follow-up at 12th week were recommended for the response. Follow-up examination includes history taking, physical examination, radiological and laboratory tests as needed.

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%

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 of 33 patients were analyzed in this study. Detailed of patient 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 the middle class and 3% belong to upper class. Among them, most of the patients (54.5%) were illiterate followed by 36.4% patients who 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% were 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 to cervical carcinoma (78.8% patients) (**Fig.1**). Other factors included taking of OCP more than 5 years (75.6%), unhealthy personal hygiene (72.7%), and multi-parity (36.4%). Clinical features was demonstrated in **Fig.2**. Most common symptom was vaginal discharge (90.9%). Other frequent symptoms were postcoital 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 a complete response while 11 patients (33.3%) had a 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 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

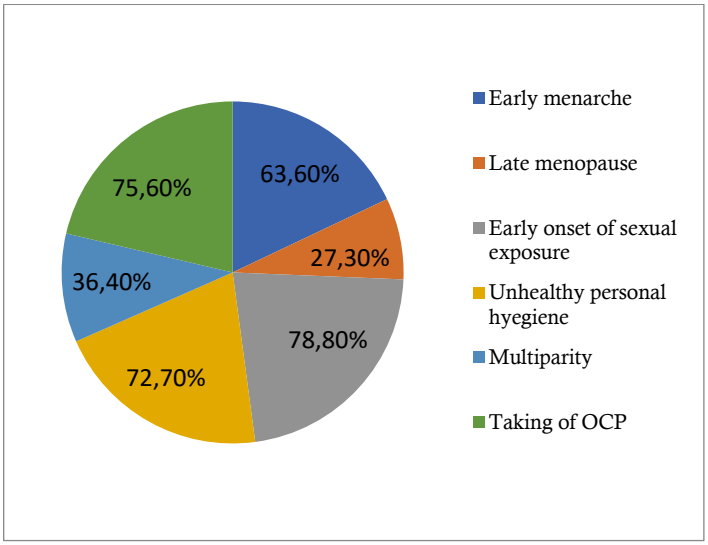

Figure 1. Risk Factors

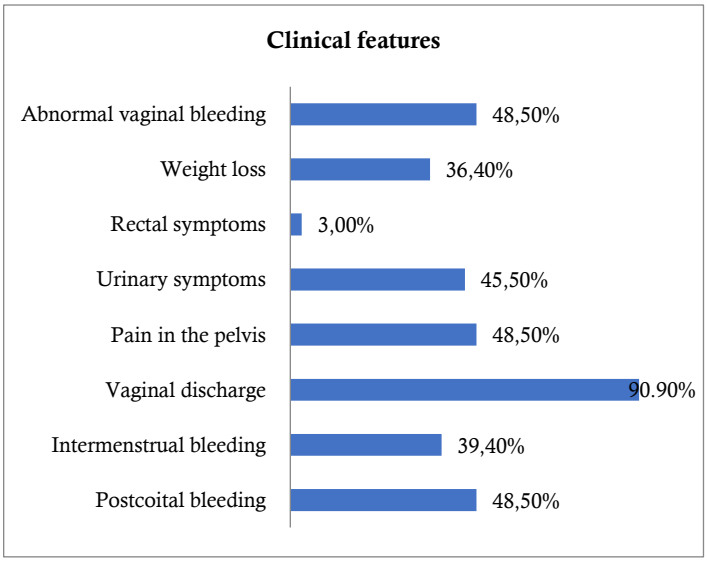

Figure 2. Clinical Features

24.2% patients showed grade 2 toxicity). The grade 1 renal toxicity was observed in 3% patients (Table 3).

DISCUSSION

Cervical cancer is one of the commonest cancers in the gynae is cervical cancer over the world. Cervical cancer treatment is a bit challenging in a developing country like Bangladesh as most of the cases are 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 the loco-regional failure rate other approaches were analysed with different regimens. Gemcitabine has a promising characteristic 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 a majority of the patients were in between middle of age group (72.7%). This observation

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

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 of cervical carcinoma (78.8%) as most of the patients got married before 16 years of age. Other factors include 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) [14], early marriage, low socio-economic condition, illiteracy, and early age of intercourse were the most common risk factors for developing carcinoma cervix and this study complies with all of these observations. Here most of the patients were in stage IIB (60.6%) and the majority of them were moderately differentiated (63.6%). This observation co Eifel et al. (2004) [15] relates with the study conducted by Thakur et al. (2018) [16]. Among all the common presenting symptoms, the most common symptom was vaginal discharge (90.9%). Other symptoms were postcoital 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 brachytherapy and according to the follow-up schedule, it was set earlier. Before 36.4% had a partial response and 3% had stable disease, CCRT 60.6% patients showed a complete response After completion of intracavitary radiotherapy (ICRT), 66.7% patients had a complete response while 33.3% patients had partial response. At the 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) [17], where in Gemcitabine arm complete response was 70%. Chufal et al. (2007) [18] 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) [19], the 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 increased rate of adverse effects [20,21]. In the study of Umanzor et al. (2006) [22] combination chemotherapy was 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) [23] the grade 2-3 dermatitis and diarrhea were higher in Gemcitabine arm, which was similar to 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 a satisfactory response rate (89%).

CONCLUSION

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 cervical cancer is concurrent chemoradiation (CCRT) with Gemcitabine is associated with considerable acute toxicity including hematological and gastrointestinal toxicity which is manageable.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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