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A Study on the Response of Concurrent Chemoradiation with Gemcitabine Versus Cisplatin in Patients with Locally Advanced Cervical Carcinoma

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Abstract

Introduction

Cervical cancer is the most common cause of cancer death in women. Currently, platinum-based concurrent chemoradiation therapy is the standard of care for locally advanced cervical cancer but treatment results are disappointing, particularly for women with bulky tumors. Several non-platinum-based agents with concurrent chemoradiation have been evolved to improve this result.

Objective

To compare the response between concurrent chemoradiation with gemcitabine and cisplatin followed by intracavitary radiotherapy in patients with locally advanced cervical carcinoma.

Material and methods

This was a quasi-experimental study, where 66 patients with untreated invasive squamous cell carcinoma of the cervix of stage IIB to stage IVA were enrolled from the Radiation Oncology Department of Rajshahi Medical College Hospital from April 2019 to March 2020. The duration of the study was 2 years. In each arm 33 patients were assigned to receive 150 mg/m² of gemcitabine (arm A) or received 40mg/m^2 of cisplatin (arm B) 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 & 47.3 years in arm A & B respectively. Most patients were in the stage IIB group (59.1% patients) and most were moderately differentiated (62.1% patients) in both arms. After 3 months of treatment, the complete response was found in 81.8% &72.7% of patients and partial response was seen in 12.1% & 18.2% of patients in arm A & B respectively (p=0.678). The grade 2 and 3 hematological toxicities (anemia, neutropenia, thrombocytopenia) were more common in arm A compared to arm B (p<0.05). The grade 2 and 3 proctitis & skin toxicity were higher in arm A & renal toxicity was higher in arm B (p=0.163).

Conclusion

Concurrent chemoradiation 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: Cisplatin**,** Cervical Cancer, Concurrent Chemoradiation, Toxicity

Introduction

Cervical cancer ranks fourth most common malignancy among women with both incidence (6.6%) and mortality (7.5%) reported by WHO on 12th September 2018 [1]. Approximately 90% of deaths from cervical cancer occurred in low and middle-income countries. The high mortality rate from cervical cancer globally could be reduced through a comprehensive approach that includes prevention, early diagnosis, effective screening, and treatment programs [2]. The disease is usually advanced by

the time of diagnosis with a high prevalence in developing countries, as reported by the New England journal of Medicine. American Cancer Society of Clinical Oncology reported on 2018 that the 5-year survival rate for all women with cervical cancer is about 67%. Cervical cancer treatment 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 [3]. A meta-analysis of individual patient data from 18 randomized trial showed chemoradiation reduces local & distant recurrence & improves disease free survival [4]. Platinum based chemotherapy improves progression free survival & reduces 30-50% risk of death in locally advanced cervical cancer [5, 6]. A recent meta-analysis of 8 randomized trial support this claim [7]. In the decade since the introduction of chemoradiation (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 [8]. To improve the survival as well as tolerability 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 [9]. It acts as a radiosensitizer at low doses & also shows synergistic effects with cisplatin [10]. Gemcitabine has been used in cervical cancer with good results both as a single agent & in combination with cisplatin concurrent with radiotherapy [11-13].

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 66 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's performance score was up to 2 and aged 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 before 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 foramen 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, a total 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

Arm - A:

Patients in the study arm (A) received concurrent chemoradiation with gemcitabine at a dose of 150 mg/m2 weekly as an intravenous (IV) infusion. It was administered 2 hours before radiotherapy. Before infusion of gemcitabine, premedication with, an antiemetic, H2 blocker, and steroids were given intravenously. Gemcitabine was diluted in 250 ml of normal saline and infused over 30 minutes. No pre- or post-hydration was given.

Arm - B:

Patients in the control arm received concurrent chemoradiation with cisplatin at a dose of 40 mg/m2 weekly as an intravenous (IV) infusion. It was administered 2 hours before radiotherapy. Before infusion of cisplatin, premedication with, an antiemetic, H2 blocker, and steroids were given intravenously. Cisplatin was diluted with 500 ml normal saline and infused over one hour. 1000 ml normal saline was given as post-chemo hydration followed by 1 amp inj. Lasix intravenously.

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 22.0 available in the institute.

Table 1: Patient's baseline characteristics

Baseline characteristics		Arm-A		Arm-B	
		N=33	%	N=33	%
Age (years)	Mean ± SD	45.36 ± 9.270		47.30 ± 8.229	
Education	Illiterate	18	54.6%	18	54.5%
	Primary	12	36.4%	12	36.4%
	SSC	3	9.1%	3	9.1%
Economic status	Lower class	27	81.8%	29	87.9%
	Middle class	5	15.2%	3	9.1%
	Upper class	1	3.0%	1	3%
ECOG performance status	PS=0,1	25	75.8%	27	81.8%
	PS=2	8	24.2%	6	18.2%
Histology grading	Well differentiated	5	15.2%	5	15.2%
	Moderately differentiated	21	63.6%	20	60.6%
	Poorly differentiated	7	21.2%	8	24.2%
Stage	Stage IIB	20	60.6%	19	57.6%
	Stage IIIA	2	6.1%	3	9.1%
	Stage IIIB	10	30.3%	8	24.2%
	Stage IVA	1	3%	3	9.1%

Table 2: Clinical Response at the end of treatment

Response	Arm A	Arm B
Response after EBRT		
CR	60.6% (20)	54.5% (18)
PR	36.4% (12)	39.4% (13)
SD	3% (1)	3% (1)
PD	0	0
Response after ICRT		
CR	66.7% (22)	60.6% (20)
PR	33.3% (11)	36.4% (12)
SD	0	3% (1)
PD	0	0
Response after 1st follow up		
CR	75.6% (25)	69.7% (23)
PR	21.2% (7)	24.3% (8)
SD	3% (1)	3% (1)
PD	0	3% (1)
Response after 2nd follow up		
CR	81.8% (27)	72.7% (24)
PR	12.1% (4)	18.2% (6)
SD	0	0
PD	6.1% (2)	9.1% (3)

CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease

Table 3: Acute Toxicity of Concurrent Chemoradiation

Toxicity	Arm-A (CCRT with gemcitabine)				Arm-B (CCRT with Cisplatin)				P-value
	No toxicity	G-I	G-II	G-III	No toxicity	G-I	G-II	G-III	
Anaemia	0	27.3%	60.6%	12.1%	18.2%	54.6%	24.2%	3%	0.003
Neutropenia	21.2%	48.5%	24.2%	6.1%	57.6%	36.4%	6.1%	0	0.005
Thrombocytopenia	75.6%	24.2%	0	0	93.9%	6.1%	0	0	0.039
Vomiting	30.3%	39.4%	24.2%	6.1%	18.2%	27.2%	36.4%	18.2%	0.209
Diarrhoea	15.2%	27.2%	42.4%	15.2%	21.2%	45.5%	24.2%	18.2%	0.265
Proctitis	0	54.5%	36.4%	9.1%	0	54.5%	36.4%	9.1%	0.598
Cystitis	0	90.9%	90.9%	0	0	90.9%	9.1%	0	0.282
Renal toxicity	87%	3%	0	0	87.9%	12.1%	0	0	0.163
Skin toxicity	0	39.4%	45.5%	15.1%	0	57.6%	33.3%	9.1%	0.137

Results

A total 66 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) years in arm A & 47.30 (SD:8.229) years in arm B. Most of the patients (81.8% vs 87.9%) came from lower economic class & were illiterate (60.6% vs 54.5%). Significant number of the patients were in stage IIB group (60.6% & 57.6% in arm A & B respectively) & (63.6% vs 60.6%) moderately differentiated. According to ECOG performance status 75.8% & 81.8% patients were in PS 0, 1 group in arm A & arm B respectively.

After completion of CCRT 60.6% & 54.5% patients showed complete response and 36.4% & 39.4% had partial response in arm A & arm B respectively. After completion of intracavitary radiotherapy (ICRT), 66.7% & 60.6% had complete response while 33.3% & 36.4% had partial response in arm A & arm B respectively. After 6 weeks of completion of treatment 75.8% & 69.7% showed complete response while 21.2% & 24.3% had partial response in arm A & B respectively. After 3 months of treatment, the

complete response was found in 81.8% & 72.7% and Partial response was seen in 12.1% & 18.2% patients and progressive disease was found in 6.1% & 9.1% patients in arm A & B respectively. Treatment response is listed in Table 2.

The acute toxicities observed during & after radiotherapy listed in Table 3. The grade 2 and 3 anaemia were higher in arm A compared to arm B, grade 2 anemia were found in 60.6% and 24.2% patients in Arm A and B respectively. The grade 2 neutropenia was more common in arm A (24.2%) compared to arm B (6.1%) & 6.1% patients had grade 3 neutropenia in arm A. The grade 1 thrombocytopenia was observed in 24.2% & 6.1% patients in arm A & B respectively. Acute hematological toxicities were higher in arm A compared to arm B and the difference was statistically significant (P value <0.05). The grade 2 vomiting were more observed in arm B than arm A, 24.2% and 36.4% patients in arm A and arm B respectively. The grade 2/3 diarrhoea and proctitis were more commonly observed in arm A compared to arm B, 36.4% patients in arm A and 27.2% in arm B showed grade 2 diarrhea, 42.4% and 15.2% patients in arm A and 24.2% and 9.1% in arm B showed grade 2 and 3 proctitis respectively. The grade 2,3 skin toxicity was more common in arm A (45.5% and 15.1%) compared to arm B (33.3% and 9.1%). Grade 2 cystitis was slightly more prevalent in arm B than in arm A (9.1% in arm A and 18.2% in arm B). Renal toxicity was higher in arm B compared to arm A (3% of patients in arm A and 12.1% of patients in arm B). These differences between two the arms were not statistically significant (P value >0.05).

Discussion

Cervical cancer is one of the most common gynecological cancers worldwide. As most of the cases presented with advanced stages due to a lack of screening and early detection programs, treating cervical cancer is a bit challenging in a developing country like Bangladesh. The standard of care for locally advanced cervical cancer is concurrent chemoradiation (CCRT) with cisplatin followed by brachytherapy [14]. Despite using concurrent cisplatin along with radiation locoregional failure rate is still high. For the improvement of locoregional failure rate other approaches were analyzed with different regimens. Gemcitabine has shown promising radiosensitising effects in clinical phase II trials [15].

This study was done from June 2018 to August 2020. The study aimed to compare the treatment outcome of concurrent chemoradiation between weekly cisplatin and gemcitabine in locally advanced cervical carcinoma. During this period patients with locally advanced cervical carcinoma were assessed for eligibility and ultimately 66 patients were included in the study after meeting inclusion criteria and giving written consent.

The mean age was 45.4 (SD ± 9.270) years (range: 25-60 years) in arm-A and 47.3 (SD ± 8.229) years (range: 30-60 years) in arm-B and most of the patients were in between 40-60 years of age group. This observation correlates with SEER 2016 and CDC statistics 2017. In the study, majority of the patients were from low socioeconomic conditions (81.8% in arm A and 87.9% in arm B). This result was also found by the study of Thakur *et al*. (2018), where women from low social classes have a higher incidence of developing cervical cancer. Here most of the patients were in stage IIB (60.6% patients in arm A and 57.6% patients in arm B), which was similar to several studies [16]. According to histopathology, all patients were squamous cell carcinoma & regarding grading of tumor, most of them were moderately differentiated (63.6% vs 60.6%). This observation correlates with the study conducted by Thakur *et al*. (2018).

After completion of CCRT 60.6% & 54.5% patients showed complete response and 36.4% & 39.4% had partial response in arm A & arm B respectively. After completion of intracavitary radiotherapy (ICRT), 66.7% & 60.6% had complete response while 33.3% & 36.4% had partial response in arm A & arm B respectively. After 6 weeks of completion of treatment 75.8% & 69.7% showed complete response while 21.2% & 24.3% had partial response in arm A & B respectively. At final assessment (3 months after completion of concurrent chemoradiation), complete response was found in 81.8% and 72.7% of patients of Arm A and Arm B, respectively. Partial response was seen in 12.1% patients in Arm A whereas for Arm B it was 18.2%. Progressive disease was found in 6.1% and 9.1% of patients in arm A and arm B respectively. Arm A had a slightly better response than arm B, but this observation was not statistically significant (p >0.05). This result correlates with the study of Verma *et al*. (2009), where the complete response was 70% in gemcitabine group and 68.8% in cisplatin group. CR was 89% in the study of Cetina *et al*. (2004) where gemcitabine dose was 300 mg/m2 [17]. In the case of a combination chemotherapy of gemcitabine and cisplatin concomitant with EBRT response rate is higher with an increased rate of adverse effects (Zarba *et al*., 2003; Hashemi *et al*., 2013) [18, 19].

During radiotherapy patients were assessed weekly for toxicity. The most prevalent acute toxicities were proctitis, cystitis, skin toxicity, and hematological toxicities (Anaemia, Neutropenia, Thrombocytopenia). There was no treatment-related mortality identified in the present study. The grade 2 anemia & neutropenia were higher in arm A compared to arm B (60.6% & 24.2% anemia & 24.2% & 6.1% neutropenia in Arm A and B respectively) & 6.1% patients experienced grade 3 neutropenia in arm A. Grade 1 thrombocytopenia was observed in 24.2% & 6.1% patients in arm A & B respectively. Acute hematological toxicities were higher in arm A compared to arm B and the differences were statistically significant (P value <0.05). The grade 2 vomiting & cystitis were more observed in arm B (36% &18.2%) than in arm A (24.2% & 9.1%) while the grade 2/3 diarrhea and proctitis were more commonly observed in arm A compared to arm B (36.4% and 27.2% with grade 2 diarrhea while 42.4% and 24.2% with grade 2 and 15.2% & 9.1% with 3 proctitis observed in arm A & B respectively). Grade 2,3 skin toxicity was more common in arm A (45.5% and 15.1%) compared to arm B (33.3% and 9.1%). Renal toxicity was higher in arm B (12.1%) compared to arm A (3%). These differences between two the arms were not statistically significant (P value >0.05). In the study of Kundu *et al*. (2008), grade 2-3 vomiting was higher in cisplatin arm, while the grade 2-3 skin toxicities & diarrhea were higher in the gemcitabine arm, which was similar with my study. In the study of Fu *et al*. (2016) the hematological & gastrointestinal toxicity were lower in CCRT with cisplatin group than other regimens [20].

From the above discussions it can be said that for the management of locally advanced cervical carcinoma,

weekly gemcitabine is comparable to weekly cisplatin concurrent with EBRT, where the complete response is higher in gemcitabine arm compared to cisplatin arm. Although the difference between two arm was not statistically significant (p-value = 0.678). The study arm showed significant haematological toxicities which was manageable. In my study cisplatin arm showed higher renal toxicity than gemcitabine arm, though it is not statistically significant. In the study of cetina *et al*. (2004) CCRT with weekly gemcitabine was given in patients with renal dysfunction and reported normalization of renal function with an excellent response rate (89%) [21].

Conclusion

Early diagnosis followed by proper management can ensure a better prognosis of cervical cancer. Furthermore, it can be said that gemcitabine can be given as an alternative to cisplatin in patients with impaired renal functions.

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