IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 7 Ver. 11 (July. 2018), PP 54-59
www.iosrjournals.org

Comparative Study of Concurrent Gemcitabine-Based Chemoradiotherapy versus Radiotherapy alone in Locally Advanced Cervical Carcinoma.

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Abstract: ***Background:*** *Carcinoma of cervix is the most common malignancy of women at our center and the majority of cases present locally advanced stages. The ability of radiotherapy alone to cure the advanced disease is limited. Therefore, need arises to increase the radiosensitivity of primary tumors. We performed this study to investigate efficacy and toxicity of gemcitabine concurrently used with radiation.* ***Methods:*** *113 cervical cancer patients were enrolled in this study and 80 eligible patients were randomized into trial-arm and control-arm. In trial-arm patients received weekly gemcitabine at dose 200mg/m^2 along with radiation and control-arm patients received radiotherapy alone. The total dose of 46 Gy in 23 fractions over a period of 4-5 weeks was given during external beam radiotherapy and 19.5 Gy (6.5 Gy per fraction/week) was given during high dose rate brachytherapy.* ***Results:*** *After three months of completion of treatment complete response was observed in 30 (75%) patients and partial response was observed in 10(25%) patients in trial-arm group as compared to that of compete response in 21(52.5%) patients, partial response in 12(%) patients, and no response in 01(2.5%) patients in control-arm group. Most frequently reported hematological adverse events in trial-arm patients were anemia 50% (20 patients) and leucopenia 30% (12 patients), while nonhematological adverse events were cystitis 15% (6 patients), proctitis 17.5% (7 patients), nausea 65% (26 patients), vomiting 50% (20 patients), and diarrhea 60% (24 patients).* ***Conclusion:*** *Even though the length of follow-up in our study was short the comparable responses have shown encouraging results. Despite initial promising results with acceptable toxicities, further large randomized study is needed to judge the efficacy of gemcitabine along with radical radiotherapy in cervical cancer patients.*

Key words: *Locally advanced cervical carcinoma, Gemcitabine, Chemoradiation, Radiotherapy.*

Date of Submission: 10-07-2018 Date of acceptance: 27-07-2018

I. Introduction:

Cervical cancer is the most frequent gynaecological cancer worldwide; the incidence of cervical cancer varies from country to country and from race to race. Globally it is second commonest malignancy in women, but in developing countries it is the commonest malignancy to affect the female population. [1, 2]

Radiotherapy is an effective treatment modality for early stages of cervical carcinoma, while in locoregionally advanced disease the ability of radiotherapy alone to cure the advanced disease is limited, because the doses required to treat large tumors exceed the limit of normal tissue tolerance. [3]

Despite improvements in radiation equipments and techniques such as hyperfractionation with increased dose, hypofractionation and variation in treatment time radiation therapy alone fails to control locoregional disease in approximately two-third cases of locally advanced cervical carcinoma. Locoregional failure is the most common cause of mortality and morbidity in these patients. [4]

Therefore, need arises to increase the radioresponsiveness of primary tumors to improve locoregional control. Many investigators have been tried to improve radiosensitivity of the tumor, such as use of hyperbaric oxygen along with radiation, particle therapy, hyperthermia, and sensitizing agents like mesonidazole but with no significant outcome. [5]

Chemotherapeutic agents also have been used for last several decades for improving the results of treatment in locally advanced disease. In such cases only concurrent chemoradiation gives better response rates and disease free survival, because the cytotoxic effect of the drug reduces the bulk of tumors, which leads to reoxygenation of the tumor and entry of the cells into a radiation sensitive phase of the cell cycle. [6]

An active drug with minimal toxicity is ideal for the treatment of locally advanced cervical carcinoma with radiotherapy. Gemcitabine is a new pyrimidine analogue which has been widely tested as a cytotoxic agent alone as well as it has shown promising results in some phase I and II trials as a radio sensitizing agent. [7-9]

We performed this single institutional study to evaluate the feasibility, efficacy, and safety profile of gemcitabine with concurrent radiotherapy for untreated locally advanced cervical carcinoma patients.

The aim of this study was to evaluate the anti tumor activity and toxicity of gemcitabine concurrently used with radiation compared with the activity and toxicity of radiotherapy alone in untreated locally advanced cervical carcinoma patients with good general condition.

II. Material And Methods:

The present study was conducted on patients reporting to Department of radiotherapy, Dr BRAM Hospital Raipur (CG).

Detailed history of patients, including age, pregnancy and parity, socioeconomic status, and previous treatment history was obtained. Complete general physical as well as pelvic examination carried out, for tissue diagnosis punch biopsy was taken from cervical growth and sent to pathology labs.

Complete blood count, renal function test, VDRL and HIV test were obtained from all the patients. For further clinical staging chest x-ray, and ultrasonography/ CT scan abdomen and pelvis were performed prior to treatment each patients.

Patients with histological proven invasive squamous cell carcinoma, stage IIB to IIIB according to FIGO (International Federation of gynecologists and obstetrics) staging system, age equal to or less than 70 years with Karnofsky performance status 80-100, with normal hematological, renal and hepatic function test, no prior treatment of present disease were eligible to this study. Study entry criteria's were shown in table-1.

Table-1 Study entry criteria of the patients.

Age	<=70 years
Performance status(KPS)	Between 80 to 100
Disease characteristic	Histologically proven squamous cell carcinoma
	Previously untreated patients
	No distant metastasis
Hematological	Hemoglobin- not <9gm%
	Total leucocytes count- not <4000/cmm
	Platelet count- <100000/cmm
Hepatic	Bilirubin- no greater than 1 mg/dl
Renal	Creatinine- < 1.5mg/dl
VDRL test	Negative
HIV test	Negative
Others	No other malignancy within past 5 years
	Not pregnant

All eligible patients were randomized into two groups: Trial-arm group patients who were subjected to concurrent chemoradiotherapy with gemcitabine and Control-arm group patients were subjected to radiation therapy alone. All of the patients signed informed consent before treatment.

Radiotherapy:

The course of radiotherapy involved a combination of external beam radiotherapy and high dose rate Intracavitary brachytherapy. Every patient of trial-arm group as well as control-arm group was treated with external beam radiotherapy (EBRT) to whole pelvis region followed by high dose rate Intracavitary brachytherapy (HDR).

The superior margin of external radiation portals was the L4-L5 interspaces and the inferiorly at the bottom of obturator foramen or the lower extension of disease and lateral margins were 1-2 cm beyond the lateral margins of the bony pelvic wall.

Pelvic radiotherapy was delivered by parallel opposed portals using a cobalt-60 (Theratron780-E) unit at a source to axis distance 80 cm. The total dose of 46 Gy in 23 fractions over a period of 4-5 weeks was given at a dose 200 centi gray per fraction daily, for 5 days in a week (Monday to Friday).

After completion of EBRT all patients were assessed for response and planned for high dose rate Intracavitary brachytherapy. HDR brachytherapy was delivered by central uterine tandem and ovoid applicators using remote after loading system with iridium -192 as its sources within 7-14 days after completion of EBRT.

The total dose of 19.5 Gy in three fractions (6.5 Gy per fraction/ week) was given to the point A. Bladder and rectal dose were limited to 80% of the prescribed point A dose as per the ICRU(international commission on radiological unit) recommendations.

Chemotherapy:

Every patients of trial-arm group were prescribed to receive gemcitabine during EBRT and HDR brachytherapy. Gemcitabine at a dose of 200 mg/m^2 was administered as 30 minutes intravenous infusion at least 4 hours before EBRT weekly on day1, day8, day15, day22, and before three sessions of HDR brachytherapy. Thus a total of 7 infusions of gemcitabine were administered during whole course of radiotherapy.

Complete blood counts and renal function test (serum blood urea nitrogen and creatinine) were evaluated weekly before consideration of chemotherapy. Depending on the severity and the duration of toxicity, the administration of gemcitabine was delayed or stopped.

The total treatment time was measured from the beginning of radiation therapy to its completion to include HDR brachytherapy, thus total duration of treatment was approximately eight weeks.

Assessment and Follow-up:

All patients in both the arms were evaluated in every week for documenting acute toxicities throughout the course of treatment. NCI common toxicity criteria were used for documentation of acute toxicities of chemoradiotherapy. Acute toxicities were defined as those occurring between the start of treatment and 90 days after treatment completion.

Late toxicities were evaluated and graded according to the Radiation Therapy Oncology Group (RTOG) especially for radiation induced adverse effects of bladder, rectum, and bowel.

Treatment responses in both the arms were evaluated after completion of EBRT and three session of HDR brachytherapy, and categorized into complete response, partial response, and no response or progressive disease. At the time of evaluation if there was complete regression of lesion, the patients were categorized into complete response.

Patients were categorized into partial response, if there was more than 50% regression in lesion in maximum diameter. If lesion regressed less than 50% in maximum diameter the patients were categorized into no response.

Patients with stable disease or no response after completion of treatment were considered for salvage surgery if resectable. Chemotherapy was administered in patients with distant metastasis or unresectable disease.

For the first six months the follow-up schedule included monthly interval, then at three months interval for two years, and then six monthly for the rest period. Patients were examined clinically and routine pelvic examination at each follow up visit. Response rate was the primary end point for analysis.

Imaging studies, including abdominopelvic ultrsonography/ computed tomography (CT), were obtained every six months for the first two years and annually thereafter. When indicated by clinical findings further investigations such as magnetic resonance imaging (MRI) were performed to identify disease progression.

III. Results:

The present study was carried on 113 patients of cervical carcinoma at the Regional cancer center Raipur (CG). Out of 113, 58 patients were in trial-arm group and 55 patients were in control-arm. Thirty three patients were excluded from analysis process due to incomplete treatment schedule, from which eighteen and fifteen patients were in trial-arm and control-arm group respectively.

Thus 80 patients could be evaluated, 40 patients received weekly gemcitabine along with radiotherapy and 40 patients received radiation therapy alone. Patients evaluated in this study belonged to age group between 30-65 years, the median age of the patient was 45 years, majority of the patients were multipara and belonged to low socioeconomic status. We did not have any patients from higher socioeconomic group.

After complete examination it is revealed that in this study 27 (33.75%) patients were stage II B and 53 (66.25%) patients were stage III B according to FIGO staging system. In this study all patients were squamous cell carcinoma, with 61 (76.25%) patients had moderately differentiated tumors and 19 (23.75%) patients had well differentiated. No patients had poorly differentiated tumors. Patient's characteristics of study subjects are shown in table-2.

Table-2 Patients' characteristic.

Patients and disease characteristic		Trial-arm patients		Control-arm patients	
		No of cases	Percentage	No of cases	Percentage
Age	30-50 years	28	70%	25	62.5%
	51-70 years	12	30%	15	37.5%
Socioeconomic status	Lower	27	67.5%	30	75%
	Lower middle	13	32.5%	10	25%
	Higher	0	0%	0	0%
Parity	01-02	02	5%	03	7.5%
	03-05	26	65%	21	52.5%
	>05	12	30%	16	40%

FIGO stage	IIB	16	40%	11	27.5%
	IIIA	0	0%	0	0%
	IIIB	24	60%	29	72.5%
Histopathology	Squamous cell carcinoma	40	100%	40	100%
Histogy grade	Well differentiated	07	17.5%	12	30%
	Mod. differentiated	33	82.5%	28	70%
	Poorly differentiated	0	0%	0	0%

Clinical Response:

All patients were assessed for response of treatment and related adverse effects after completion of treatment. When response was observed just after completion of treatment, in trial-arm group 65% (26) patients were disease free and 35% (14) patients were residual disease. While in control-arm group 22.5% (9) patients were disease free and 77.5% (31) patients were residual disease.

After three months of completion of treatment complete response was observed in 75% (30) patients and partial response was observed in 25% (10) patients in trial-arm group as compared to that of compete response in 52.5% (21) patients, partial response in 30% (12) patients, and no response in 2.5% (01) patients in control-arm group.

When response was observed according to stage of the disease 12(81.25%) patients out of 16 of stage IIB had complete response in trial-arm, and 07(63.64%) patients out of 11 had complete response in control-arm. In stage IIIB, 17 (70.83%) patients out of 24 had complete response in trial-arm, and 13(44.82%) patients out of 29 had complete response in control-arm.

Thus a direct correlation between bulk of the disease and tumor response, as stage increase from stage IIB to IIIB complete response went down in both arms.

When response was evaluated after six months follow-up 60% (24) patients had locoregional control and 15% (06) patients had persisting locoregional disease in trial-arm patients, as compared to that of 47.5% (19) patients had locoregional control and 30% (12) patients had persisting disease in control-arm group. In trial-arm 30 out of 40 patients and in control-arm 31 out of 40 patients regularly came for monthly follow-up till six months. Responses of treatment are shown in Table-3 & 4.

Table-3 Responses of treatment

Response terminology	**Response after 03 months of completion of treatment**			
	Trial-arm		Control-arm	
	No of patients	Percentage	No of patients	Percentage
Complete response	30	75%	21	52.5%
Partial response	10	25%	18	45%
No response	0	0%	01	2.5%
Response terminology	**Response after 06 months of completion of treatment**			
	Trial-arm		Control-arm	
	No of patients	Percentage	No of patients	Percentage
Complete response	24	60%	19	47.5%
Partial response	06	15%	12	30%
No response	0	0%	0	0%

Table-4 Response according to stage of disease.

Response terminology	**Stage II B**				**Stage III B**			
	Trial-arm (16 pts)		Control-arm (11 pts)		Trial-arm (24 pts)		Control-arm (29 pts)	
	Pts	%	Pts	%	Pts	%	Pts	%
Complete response	13	81.25%	07	63.64%	17	70.83%	13	44.82%
Partial response	03	18.75%	04	36.36%	07	29.16%	15	51.72%
No response	0	0%	0	0%	0	0%	01	3.44%

Adverse Events:

Gemcitabine based chemoradiation and radiotherapy alone were well tolerated by the patients. All patients were assessed for acute toxicities of chemoradiation and radiation alone during and after completion of treatment.

As expected the hematological and gastrointestinal toxicities were higher in patients treated with chemoradiation (trial-arm) than that of patients treated with radiotherapy alone (control-arm). There was no treatment related morbidity.

Most frequently reported hematological adverse events in trial-arm patients were anemia 50% (20 patients) and leucopenia 30% (12 patients), while nonhematological adverse events were cystitis 15% (6 patients), proctitis 17.5% (7 patients), nausea 65% (26 patients), vomiting 50% (20 patients), and diarrhea 60% (24 patients).

In control-arm patients hematological toxicities observed were anemia 45% (18 patients), and leucopenia 22.5% (9 patients), while nonhematological adverse events were cystitis 5% (2 patients), proctitis 7.5% (3 patients), nausea 45% (18 patients), vomiting 25% (10 patients), and diarrhea 30% (12 patients).

Most of these toxicities were mild (grade I and II) and mange with supportive care without interruption of treatment. No grade III or IV hematological and nonhematological acute toxicity was observed in this study. Acute toxicities of treatment are shown in table-5.

Table-5 Acute toxicity of Chemoradiotherapy versus Radiotherapy alone.

Toxicities	Trial-arm Patients						Control-arm Patients					
Hematological	Grade				Total	Total	Grade				Total	Total
	I	II	III	IV	Pts	%	I	II	III	IV	Pts	%
Anemia	17	03	0	0	20	50%	18	0	0	0	18	45%
Leucopenia	10	02	0	0	12	30%	09	0	0	0	09	22.5%
Nonhematological	Grade				Total	Total	Grade				Total	Total
	I	II	III	IV	Pts	%	I	II	III	IV	Pts	%
Nausea	20	06	0	0	26	65%	18	0	0	0	18	45%
Vomiting	16	04	0	0	20	50%	10	0	0	0	10	25%
Diarrhea	19	05	0	0	24	60%	12	0	0	0	12	30%
Cystitis	04	02	0	0	06	15%	02	0	0	0	02	05%
Proctitis	05	02	0	0	07	17.5%	03	0	0	0	03	7.5%

IV. Discussion:

Cervical cancer is a highly curable disease when diagnosed in its early stage. In India due to the lack of screening and early detection programs, 70% to 80% of the women with cervical cancer are diagnosed with locally advanced disease where uncontrolled locoregional pelvic disease is the cause of morbidity. [10]

Although radiation therapy is a sole treatment could provide a good result for early stage cervical carcinoma, the longer survival rate for patients with locally advanced disease treated with radiation alone is limited, despite improvements in radiotherapy techniques and equipments. [11]

Thus locoregional control is of paramount importance to improve survival. Therefore many methods have been tried to improve the radiosensitivity of the tumor, but only concurrent chemoradiation gives better response rates, disease free survival and overall survival in such cases. [12]

Present study provides follow-up of patients of locally advanced cervical carcinoma treated with gemcitabine based concurrent chemoradiation and radiotherapy alone. Our goal was to evaluate efficacy and toxicity of gemcitabine concurrently used with radiotherapy.

Similar to the findings of other authors, in this study we also found that gemcitabine based chemoradiotherapy was well tolerated by the patients and toxicities were manageable. All patients were assessed for acute toxicity of chemoradiation and radiation alone during and after treatment.

The toxicities observed in trial-arm and control-arm were similar in pattern, most of them were mild to moderate, and manageable by medications thereby no interruption in the treatment.

The overall complete response rate was 63.75% (51/80), and partial response rate was 35% (28/80), with 1.25% (01/80) had stable disease or no response to treatment after three months of follow-up. Twelve (81.25%) patients out of 16 of stage IIB had complete response in trial-arm, and seven (63.64%) patients out of 11 had complete response in control-arm.

In stage IIIB, Seventeen (70.83%) patients out of 24 had complete response in trial-arm and thirteen (44.82%) patients out of 29 had complete response in control-arm, respectively. We found that there was a correlation between bulk of the disease and complete response, as the tumor bulk increased the response rate dropped down in both arms.

It has been reported that patients from low socioeconomic status and parity have a greater cervical cancer incidence and present with more advanced stage, as well as lower rates of survival. [13] The same is observed in our study as shown in table-2 that 47(58.75%) patients had 03-05 children and 28 (35%) patients had more than 05 children, as well as 57 (71.25%) patients belonged to low socioeconomic group.

In the literature reviewed various studies have shown a beneficial effect of concurrent use of gemcitabine with radiation. A study has been published by Mc Cormack et al investigating the use of gemcitabine and radiation therapy in patients with advanced cervical cancer. 10 patients received gemcitabine on days 1, 8, 15, 22, 29, and 35 concurrently with radiation up to 50.4 Gy (28 fractions) over 5.5 weeks. The dosage of gemcitabine was 50 mg/m^2 (3 patients), 100mg/m^2 (3 patients), and 150 mg/m^2 (4 patients). [14]

In a study by P. Patttaranutaporn et al 19 patients with stage IIIB cervical cancer were treated with gemcitabine (300 mg/m^2) and standard radiotherapy. Complete responses were observed in 17(89.5%) patients, one partial response and one no response to treatment. Grade 3 toxicity included anemia and diarrhea, other toxicity included grade 1 or 2 nausea and vomiting (8 patients), proctitis (2 patients), and cystitis (8 patients). [15]

Porras et al conducted a trial of gemcitabine 350 mg/m^2 weekly for 5 weeks, concurrently to external radiotherapy followed by brachytherapy in 24 patients with IB2-IVA disease. Two patients were discontinued from the protocol. Overall response was observed in 22 patients.

In the above studies different doses of gemcitabine as a single agent ranging from 50 mg/m^2 to 350 mg/m^2 have been used. In our study gemcitabine was used at a dose of 200 mg/m^2 which was well tolerated. The results of this study were comparable to studies carried out by Mc Cormack and P. Patttaranutaporn regarding the similarity in staging of the disease, and dosing schedule of gemcitabine and radiotherapy.

Even though the length of follow-up in this study was short as compared to other studies the comparable responses and survival have shown encouraging results. However larger randomized study and longer follow-up will be required to define the disease free survival and overall survival.

V. Conclusion:

The regimen of concurrent chemoradiotherapy with gemcitabine was well tolerated by the patients of locally advanced cervical carcinoma. While comparing the results of trial-arm with control-arm it was found that gemcitabine is safe and effective against locally advanced disease.

Complete response rate was higher in trial-arm patients as compared to control-arm patients in both stages. Most important factor affecting the complete response in our study was stage of the disease.

Even though the length of follow-up in our study was short the comparable responses have shown encouraging results. However large randomized, multi institutional study and longer duration of follow-up is needed to reach any form of conclusion.

Acknowledgement

The authors would like to thanks, Director Professor Vivek Choudhary, Director Regional Cancer Center, Raipur, Chhattisgarh, India, for his continuous encouragements and support for this study.

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