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Oncology

TREATMENT RESULTS OF CARBOPLATIN BASED CONCURRENT CHEMORADIATION FOR LOCALLY ADVANCED CERVICAL CARCINOMA.

Dr Suresh Kumar Thakur* Associate Professor, Department of Radiotherapy, Govt Medical College Jagdalpur (CG). *Corresponding Author

Dr S K Azad Professor, Department of Radiotherapy, Regional Cancer Center Raipur (CG).

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 aim of this study was to assess the efficacy and toxicity of carboplatin based concurrent chemoradiation in patients with locally advanced cervical carcinoma.

Methods: Fifty seven locally advanced cervical cancer patients were enrolled in this study and fifty eligible patients were received weekly carboplatin at dose of area under curve 2, along with radical radiotherapy. The total dose of 50 Gy in 25 fractions over a period of 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 two months of completion of treatment the complete response rate was observed in 37(74%) patients, with 11 (22%) patients had partial response and 02 (04%) patients had stable disease or no response to treatment. The hematological toxicities with grade III were observed in 06(12%) patients and grade IV observed in 02(04%) patients.

Conclusion: Despite initial promising results with acceptable toxicities, further large randomized study is needed to judge the efficacy of carboplatin along with radical radiotherapy in cervical cancer patients.

KEYWORDS : Carboplatin, Concurrent Chemoradiation, Locally Advanced Carcinoma Cervix.

INTRODUCTION:

Carcinoma of uterine cervix is the second most common cause of cancer related morbidity and mortality among women in developing countries including India. However reported incidences and mortality rates show wide geographic variation. [1-2]

In India almost 70% to 80% patients are diagnosed with locally advanced disease. The majorities of these patients are not candidates for surgery but are suitable for radiotherapy. However in spite of all efforts, and improvements in radiation equipment and techniques, radiotherapy alone has not significantly improved the survival rates. [3]

For improving the results of treatment in locally advanced cervical cancer, chemotherapeutic agents have been used for 3-4 decades. It has been used as neo-adjuvant, adjuvant and concurrent chemo-radiation. In such cases concurrent chemo-radiation is attractive concept in which chemotherapy is utilized primarily to sensitize tumor cells to radiotherapy and increase loco-regional control; it gives better response rates, disease free survival and overall survival. [4-5]

At present cisplatin-based chemoradiotherapy is the standard treatment for patients with locally advanced cervical carcinoma. Weekly cisplatin is the most commonly used regimen for chemoradiation and relatively well tolerated; it improves survival and raises local control rates up to 80%. [6-7]

However, its high emetogenic effects, potential nephrotoxicity, low compliance as well as the administration of cisplatin need for a large amount of hydration could result in hesitation over its use, particularly in patients with renal dysfunction, such as those with ureteral obstruction in advanced cervical cancer.

Carboplatin is a platinum analog that was introduced in 1981, which is a less nephrotoxic, neurotoxic and emetogenic than cisplatin, and also an effective radiosensitizer both in vivo and in vitro, targeting hypoxic cells populations and enhancing cell killing by radiation, moreover the administration of carboplatin is generally easier than cisplatin. [8-9]

Many studies reported the experiences of carboplatin based chemoradiotherapy in the treatment of locally advanced cervical cancer patients, with favorable toxicity profile and better patient adherence to treatment plan. [10-14]

Carcinoma of cervix is the most common malignancy of women at our center and the majority of cases are locally advanced at diagnosis; hence, we performed this observational study to evaluate the disease related outcomes and therapy-related toxicities of carboplatin based concurrent chemoradiotherapy for locally advanced cervical cancer patients.

MATERIAL AND METHODS

The present study was conducted on locally advanced cervical cancer patients reporting to Department of Radiotherapy, Regional Cancer Center, Raipur (C.G.) India, from August 2011 to July 2012.

Eligibility criteria included patients must have histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of cervix, with FIGO (International federation of gynecologists and obstetrics) stage IIB-IIIB, Karnofsky performance status >=70. Patients must have no prior exposure to chemotherapy, radiotherapy, or surgery, and no significant hematological, hepatic or renal impairment as judged by standard hematological and biochemical investigations.

Patients with age >70 years or <18 years, FIGO stage < IIB or > IIIB, sever co-morbidity with Karnofsky performance status <70%., previous chemotherapy, radiotherapy or surgery, pregnancy or distant metastasis at diagnosis and history of allergies were excluded from the study.

All patients were examined clinically including thorough pelvic examination under anesthesia and document disease status according to the FIGO staging system.

All patients were investigated with baseline hematological and biochemical examination before treatment. Chest x-ray and ultrasound/C.T. abdomen and pelvis were performed prior to treatment of each patient. Written consent was obtained from all patients before treatment.

RADIOTHERAPY:

Radiotherapy involved a combination of external beam radiotherapy (EBRT) and high dose rate Intracavitary brachytherapy (ICBT). All patients received whole pelvic radiotherapy to the primary tumor and pelvic lymph nodes by conventional radiotherapy using linear accelerator with 6MV photons. The upper margin of external radiation portals was the L4-L5 junction and the lower margin was 3 cm below the palpable cervical growth or up to the introitus if the vagina was involved. Lateral margins were 1.5-2 cm lateral to the brim of the lesser pelvis.

The dose of 50 Gy in 25 fractions over a period of 5 weeks was given at dose of 200 centi gray per fraction daily, for 5 days in a week (Monday to Friday). After completion of 46 Gy, central shielding was added to reduce the bladder and rectal dose. All the patients were instructed to keep the urinary bladder full during EBRT.

After completion of EBRT patients were assessed for response and planned for high dose rate ICBT within 7 to 14 days. Patients with good local response and preserved local anatomy were subjected to high dose rate ICBT, and were given three fractions of high dose rate ICBT with a weekly interval using a remote after loading system with iridium 192 as its source.

The total dose of 19.5 Gy in three fractions (6.5 Gy per fraction/week) was prescribed 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.

Patients with poor response or not fit for Intracavitary brachytherapy were given external beam radiotherapy with reduced field size with a total dose of 60-66 Gy, with or without chemotherapy depending upon treatment related toxicities.

CONCURRENT CHEMOTHERAPY:

All patients were prescribed to receive carboplatin during EBRT and ICBT. The chemotherapy started at the beginning of EBRT and was administered at weekly interval for maximum of 5 cycles during the course of EBRT. Additional 3 cycles of weekly carboplatin was given before ICBT. The total treatment time was measured from the beginning of radiation therapy to its completion to include ICBT, thus total duration of treatment was approximately 8-9 weeks.

Glomerular filtration rate (GFR) was calculated from patient's serum creatinine, age and body weight and the dose of area under curve (AUC) equal to 2 was calculated from the GFR by using Calvert's formula.[15] The maximum dose of carboplatin for each cycle was not more than 150 mg .

Complete blood counts and renal function test (serum blood urea nitrogen and creatinine) were evaluated weekly and the dose of carboplatin was modified according to hematological and biochemical investigation prior to each cycle of chemotherapy. Depending on the severity and duration of toxicity, the administration of carboplatin was delayed or stopped.

ASSESSMENT AND FOLLOWUP:

All the patients were assessed in every week for documenting acute toxicities and every 2 weeks for disease response throughout the course of chemoradiotherapy. Acute toxicities were defined as those occurring between the start of treatment and 90 days after treatment completion.

NCI Common toxicity criteria version 3.0 was used for monitoring and documentation of acute toxicities of treatment. Late toxicities were evaluated and graded according to the Radiation Therapy Oncology Group (RTOG) especially for radiation-induced complications of bladder, rectum, and bowel.

Patients were assessed for disease response and categorized into complete response, partial response, and no response or progressive disease. 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. Response terminologies are shown in Table-1.

Table-1 Response was registered in terms of:-

Response group	Description
C.R. (Complete response)	No clinical evidence of disease/complete regression of disease at primary site and regional lymph node.
P.R. (Partial response)	More than 50% regression in lesion in maximum diameter.
N.R. (NO response)	If the lesion regressed less than 50% in maximum diameter.
P.D. (Progressive Disease)	Increase in size of tumor or appearance of secondaries.

The follow-up schedule included monthly interval for the first 6 months then at 3 month interval for the rest period. Patients were examined clinically and routine pelvic examination at each follow up visit. Further investigations such as cervical cytology, chest x-ray, abdominopelvic sonography, and CT/MRI were performed when indicated by clinical findings to identify disease progression.

RESULT:

From August 2011 to July 2012, total 57 patients of carcinoma cervix were enrolled for the study. We offered nonsurgical treatment consisting of radiation therapy with or without concurrent carboplatin to all patients. Five patients declined to receive chemotherapy and two patients had received treatment with different protocol. Consequently 50 patients were received their carboplatin based chemoradiotherapy and were analyzed for local control, local recurrence, disease progression, and treatment related complications.

Patients evaluated in this study belonged to the age ranging from 27 to 65 years with the median age of 45 years. Majority of the patients had ulceroproliferative growth, and 45 (90%) patients were diagnosed as squamous cell carcinoma, 03 (06%) patients had adenocarcinoma and 02 (04%) patients had adenosquamous cell carcinoma.

After complete clinical and radiological examination it is revealed that 23 (46%) patients were stage IIB and 27 (54%) patients were stage IIIB according to FIGO staging system. Patient's characteristics of study subjects are shown in Table-2.

Table-2 Patients' characteristics.

Patients and disease characteristics		No of cases	Percentage
Age	Range 27-65 years (Median 45 years)	50	100 %
Types of growth	Ulceroproliferative	40	80%
	Non proliferative	09	18%
	Infiltrative	01	02%
	Nodular infiltrative	00	0%
Histopathology	Squamous cell carcinoma	45	90%
	Adenocarcinoma	03	06%
	Adenosquamous carcinoma	02	0%
FIGO stage	IIB	23	46%
	IIIA	00	0%
	IIIB	27	54%
Parity	01 to 02	14	28%
	03 to 05	24	48%
	>=05	12	24%
Hemoglobin (Pretreatment)	09 to 12	31	62%
	>12	19	38%

Clinical Response:

All the patients were examined after completion of treatment for the evaluation of response to chemoradiation and related complications. When response evaluation was done just after completion of treatment, the overall response rate was observed in 47(94%) patients, 03(06%) patients had stable disease or no response to treatment. After completion of treatment all patients were kept on close monthly-follow up.

After two months of completion of treatment the overall complete response rate was observed in 37(74%) patients, with 11(22%) patients had partial response, and 02(04%) patients had stable disease or no response to treatment. When response was observed according to stage, in stage IIB 19(82.60%) patients out of 23 had complete response while in stage IIIB, 18(66.67%) patients out of 27 had complete response, It has been observed that earlier the stage of the disease better is the response, as stage increases from stage IIB to stage IIIB complete response went down.

After nine months of completion of treatment the overall complete response rate was seen in 33(66%) patients, with 15 (30%) patients had locoregional disease, and 01 (02%) patient had no response to treatment, and 01 (02%) patient had distant metastasis along with locoregional disease. Responses of treatment are shown in Table-3.

Table-3 Response of Chemoradiotherapy.

Response after 02 months of chemoradiotherapy						
FIGO	Stage IIB		Stage IIIB		Total	Total
Response	Patients	Percentage	Patients	Percentage	Patients	Percentage
C.R.	19	82.60%	18	66.67%	37	74%
P.R.	04	21.73%	07	22.23%	11	22%
N.R.	00	0%	02	7.4%	02	04%
P.D.	00	0%	00	0%	00	0%
Response after 09 months of chemoradiotherapy						
FIGO	Stage IIB		Stage IIIB		Total	Total
Response	Patients	Percentage	Patients	Percentage	Patients	Percentage
C.R.	17	73.91%	16	59.26%	33	66%
P.R.	06	26.09%	09	33.34%	15	30%
N.R.	00	0%	01	3.70%	01	3.70%
P.D.	00	0%	01	3.70%	01	3.70%

C.R. =Complete response, P.R. =Partial response, N.R. =No response, P.D. =Progressive disease.

Adverse Events:

All patients were monitored for acute toxicities during the course of

chemoradiotherapy. There was no treatment related morbidity. The most common observed hematologic adverse events of treatment were anemia, neutropenia, leucopenia, and thrombocytopenia. The most frequently reported non-hematologic adverse events were nausea, vomiting, diarrhea, and fatigue. Most of these toxicities were mild (grade-I & grade-II) and manage with supportive care without interruption of treatment.

The hematologic toxicities with grade III were observed in 06(12%) patients and grade IV were observed in 02(04%) patients, and managed by injection GCSF (granulocyte colony stimulating factor), packed cell transfusion, or platelet transfusion as indicated.

Late complication involving bladder and rectum according to RTOG criteria were found in 07(14%) patients after six months of completion of treatment. Two patients had grade I and one patient had grade II cystitis, while two patients had grade I and two patients had grade II radiation proctitis. Patients with cystitis were managed by bladder irrigations and urinary analgesics, and patients with proctitis were managed symptomatically with stool softeners and steroid enemas. Acute and late toxicities of treatment are shown in table-4.

Table-4 Acute and Late toxicities of chemoradiotherapy.

Acute toxicities of treatment						
Hematologic	**Grade**				**Total Patients**	**Total Percentage**
	I	II	III	IV		
Anemia	18	04	03	01	26	52%
Leucopenia	10	07	02	01	20	40%
Neutropenia	08	06	01	00	15	30%
Thrombocytopenia	09	05	00	00	14	28%
Non hematologic	**Grade**				**Total Patients**	**Total Percentage**
	I	II	III	IV		
Nausea	10	03	00	00	13	26%
Vomiting	08	02	00	00	10	20%
Diarrhea	03	02	00	00	05	10%
Fatigue	11	02	00	00	13	26%
Late toxicities of treatment						
RTOG Criteria	Grade				Total Patients	Total Percentage
	I	II	III	IV		
Cystitis	02	01	00	00	03	06%
Proctitis	02	02	00	00	04	08%

DISCUSSION:

The treatment options of cervical cancer are composed of surgery, radiotherapy and/or chemotherapy, according to stage and performance status of the patients. For early stage cervical cancer radical radiotherapy or curative surgery both are equally effective with excellent disease control and long term survival, while in locally advanced disease is still difficult to treat. In more advanced tumor radiation therapy alone fails to control local disease due to propensity for local recurrence and distant metastatic spread. [16-17]

Therefore treatment of locally advanced cervical carcinoma requires systemic treatment such as chemotherapy in addition to standard radiation treatment. After publication of several randomized clinical trial concurrent chemoradiotherapy has now become an integral part of standard treatment of patients with locally advanced cervical carcinoma. [18-20]

We conducted this study to evaluate the feasibility and tolerability of concurrent carboplatin along with radical radiotherapy in our clinical settings, where patients usually present with locally advanced stages. Similar to the findings of other authors, in this study we also found that carboplatin based chemoradiotherapy was well tolerated by the patients and toxicities were manageable.

The overall complete response rate was 74% (37/50), and partial response rate was 22% (11/50), with 02% (01/50) had stable disease or no response to treatment after two months of follow-up. We meditate about some reasons for the low complete response rate in our study. We found that patients with more advanced disease was affect the response rate, the complete response in stage IIB disease was 73.91% as compared to only 59.26% in stage IIIB disease after nine months of follow-up.

We also noted that most of our patients were not received their treatment (EBRT and ICBT) within 8-9 weeks. The common reason why most of the patients were not completed their treatment on time was their low socioeconomic status, illiteracy, and poor devotion to the scheduled treatment visits.

The present study results in our patients are acceptable considering the fact that all of our patients had locally advanced cancer of cervix stage IIB-IIIB. Effectiveness of the treatment modality was judged not only by the objective response of the tumor but also by the associated side effects. Since both the radiation and chemotherapy have an adverse effect on normal tissue, there is an increased incidence of acute toxicities in the treatment.

In the present study acute toxicities were mostly hematological and of these anemias was the commonest. One (02%) patient developed grade IV and three (06%) patients developed grade III anemia and had to receive blood transfusion in addition to oral iron supplementation.

Nausea and vomiting was the most common non hematological toxicities of our patients, as well as grade II radiation proctitis were found in two (04%) patients and grade II cystitis was found in one (02%) patient as late toxicities.

A study has been published by Higgins et al, evaluated 31 patients treated with carboplatin based chemoradiotherapy at dose area under curve of 2, which is similar to our study. They reported that objective tumor response based on physical examination and computed tomography measurements was 90%. Only three patients developed grade III leucopenia, one patient developed grade III neutropenia, and two patients developed grade III thrombocytopenia. [21]

Though the dose and schedule of carboplatin has similar in both studies, the results presented by above study may not be comparable to our study because in our study high dose rate brachytherapy has been used but they used low dose rate brachytherapy after completion of EBRT.

Other study by Dubey et al reported 21 patients treated with carboplatin at dose of 300 mg/m^2 every 3 week along with radiation therapy, with a pelvic control rate of 76% and overall survival of 71%. Only one patient developed grade III gastrointestinal toxicity, and two patients developed grade III anemia, and two patients developed grade III granulocytopenia.[22] Hematological and nonhematological acute toxicities developed by the patients in both studies are almost similar, though the dose and schedule of carboplatin have different in both studies.

We recognize that our studies has certain limitations, like it was not included standard treatment to comparison, it is single institutional study and patients number was small to achieve statistically significant result. Our intention was to report our experience with carboplatin based chemoradiotherapy in patients with locally advanced cervical carcinoma, where response rate was the primary end point for analysis. Despite the mentioned limitations, the present study showed good results in terms of overall response and complete response. In addition, the compliance was better and acute toxicities were lower in terms of hematological and nonhematological. However the large randomized controlled multicenter studies are required to overcome these limitations.

CONCLUSION:

In conclusion, the study results have shown that carboplatin based concurrent chemoradiation was well tolerated by the patients of locally advanced cervical carcinoma with acceptable toxicities.

Even though the small sample size and the length of follow up in our study were short, the study results encourage the use of carboplatin along with radiation in cervical cancer patients.

Despite the initial promising results and acceptable toxicities, a large randomized multicenter studies and longer follow up is needed to reach the any form of conclusion.

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