



CARCINOMA CERVIX- STUDY TO EVALUATE THE RESPONSE AND TOXICITY OF TELETHERAPY WITH CONCURRENT WEEKLY CARBOPLATIN VERSUS RADIATION THERAPY ALONE.

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ABSTRACT **Objective:** To assess the clinical response and toxicity of concurrent treatment of external beam radiotherapy (EBRT) with carboplatin to external beam radiotherapy alone in cervical cancer. **Method and material:** Total 40 patients divided into two arms with 20 patients received EBRT with concurrent chemotherapy with weekly carboplatin 150mg and rest 20 patients received EBRT alone. Prescribed radiation dose to both the arms was 46 gray (Gy) in 20 fractions (#) in four weeks, 2.3Gy/# for five days in a week. concomitant weekly carboplatin given to the patient 4 to 5 hours before the radiation. **Result:** Complete response found in 15 patients (75%) in arm-A and 8 patients (40%) in arm-B along with productive gain in symptoms. Haematological toxicity and high-grade skin toxicity found in a greater number of patients in study arm. **Conclusion:** On the basis of study concluded that Patients with cervix cancer can be treated on schedule with concurrent carboplatin with EBRT. This regimen is well tolerated and produces excellent response rates and acceptable toxicities.

KEYWORDS : Carcinoma cervix, Concomitant chemotherapy, radiotherapy

INTRODUCTION

Carcinoma cervix is a common malignancy affecting female population in our country. Approximately 80% of total cases occur in developing countries. Carcinoma of the uterine cervix is the most common cancer in Indian women and occupies the top rank among cancers in women in most developing countries, constituting 38% of all women's cancers. To an estimated annual global incidence of 6,04,127 (3.1%) cervical cancers, India have about 1,00,000 cases, contributes 1/6 of the worlds burden. while gravity of the problem is thus more than evident. The world pattern of cervical cancer, together with the age adjusted rate and ranking, clearly indicate that cervical cancer is predominantly a problem of poorer socio-economic societies.^[1]

It is more common in women with early initial sexual activity and/or multiple sexual partners, and in smokers. Venereal transmission of human papilloma virus (HPV) has important etiologic role. A number of factors may influence the choice of local treatment for cervical cancer, including tumor size, stage, histologic features, evidence of lymph node metastasis, risk factor for complications of surgery or radiotherapy, and patient preference. Smegma of the man also is said to contribute in the development of carcinoma cervix. Incidence of carcinoma cervix is 23% higher in fertile Women than infertile women. Similarly single, widowed, divorced women were found to have smaller percentage of carcinoma cervix. Second wife of a man whose first wife died from carcinoma cervix has higher risk of developing carcinoma cervix.^[2]

The prognosis of this disease is directly related to the stage at presentation. Surgery or radical radiotherapy (RT) in the early stages of disease (stage IA-IIA) results in cure in more than 80% of women, five-year survival rate is 60% for stage IIB, 30-35% for stage III and <15% for stage IVA disease following radiotherapy. Loco-regional recurrence (seen in 40% to 70% of patients) is the main cause of failure in post radiation and about 20% patients fail due to distant metastasis.^[3] Radiotherapy is the sole treatment for advanced cases of cancer cervix. After the initial fractions of radiotherapy there occurs a procession of events in the tumour mass i.e. the cell killing, elkind recovery, removal of cell debris by it lysis and absorption. It results in shrinkage of tumor mass better oxygenation of remaining component of tumor cells. A shift of hypoxic cell to the oxygenated compartment increases the radiosensitivity of cancer cells and lastly the repopulation of the cells, both normal and malignant.^[4]

The prevalence and burden of cervical cancer is much higher among Women of low socioeconomic status as well as among rural women in India. The primary reason given for this is lack of access to screening and health services, and lack of awareness of the risk factors among rural women in India. The primary reason given for this is lack of access to screening and health services, and lack of awareness of the risk factors of cervical cancer. HPV infection and precancerous lesions go unnoticed and develop into full blown cancer before women realise

they need to go for medical help Moreover, due to difficulties of access and affordability, compliance to, and follow up of, treatment is much worse for women of low Socioeconomic status, leading to further morbidity and mortality from the disease.^[5]

In this study we evaluate the response of external radiotherapy with concurrent weekly carboplatin in carcinoma cervix. Carboplatin has been reported to enhance the cytotoxicity of radiation in a number of studies in both, the cell culture and the tumor bearing animals. The precise biochemical mechanism of this interaction has not been defined although inhibition of repair of sublethal damage by carboplatin has been postulated to occur Also carboplatin is the most active cytotoxic agent in advance, metastatic and recurrent squamous cell carcinoma of the cervix. Carboplatin is less nephrotoxic and less neurotoxic than cisplatin.^[6]

In this study evaluate the clinical response and toxicity of concurrent carboplatin with external beam radiotherapy to external beam radiotherapy alone in carcinoma of cervix.

METHOD AND MATERIAL

A detailed history regarding age, sex, religion, occupation, addiction, gravida, parity, presenting complaints, their duration and past history was obtained from each patient followed by a thorough General examination Local examination and Gynaecological examination. This was done before the instigation as well as during and after the completion of treatment. Pre-treatment work up as Complete blood count, Blood Urea, Blood Sugar, X-Ray Chest PA View, USG abdomen & pelvis and CT Abdomen. Patients were staged according to FIGO classification. All patients were explained the nature of treatment, its duration, efficacy, and the side effects, they were likely to face.

In current study, total 40 patients were segregated into two arms with 20 patients in each. In arm-A, 20 patients had received EBRT along with Concomitant chemotherapy with weekly carboplatin 150mg and in arm-B, EBRT alone was delivered. Both the groups received 46 Gy in 20# in four weeks, with 2.3Gy/# daily from Monday to Friday with interval of last two days of week. Concomitant weekly carboplatin 150mg, given to the patient 4 to 5 hours before the radiation, in arm-A.

RESULT

The table shows that Squamous cell carcinoma is the most common histopathology found in Carcinoma Cervix. Details given in table number 1.

Table 1. Distribution of histopathological type

Type	No. of patient	Percentage
Squamous cell Carcinoma	33	82.5%
Adenocarcinoma	4	10%
Adeno-squamous carcinoma	3	7.5%
Total	40	100%

The table shows that maximum number of patients was from stage IIIB. Details are given in table number 2.

Table 2. Distribution according to clinical staging wise

Type	No. of patient	Percentage
IIIB	29	72.5%
IIB	8	20%
IIA	3	7.5%
Total	40	100%

Evaluating all the patients in this study found that in arm-A, 15 patients (75%) experienced complete response in association with resolution of symptoms and 5 patients (25%) experienced partial response. 2 patients with partial response are improving further and 3 patients are being maintained in partial response and 4 responder has relapsed during therapy. Amongst arm-B, 8 patients (40%) experienced complete response in association with resolution of symptoms and 10 patients (50%) experienced partial response and 2 patients (10%) had no response. Details given in table number 3.

Table 3. Response of two different treatment schedules

Arm	No. of patients		
	Complete response	Partial response	No response
Arm-A	15	5	0
Arm-B	8	10	2
Total	23	15	2

The table shows maximum number of patients had Grade I and Grade II toxicity. Details have been given in table number 4.

Table 4. Skin reaction grading

Arm	No. of patient		
	Grade 1	Grade 2	Grade 3
Arm-A	4	11	5
Arm-B	7	12	1
Total	11	23	6

Myelosuppression demonstrated in 45% (9 out of 20) patients from study arm-A and 15% (3 out of 20) patients in arm-B. Details given in table number 5.

Table 5. haematological toxicity (myelosuppression)

Arm	No. of patient	Percentage
Arm-A	9	45%
Arm-B	3	15%

DISCUSSION

As the scenario in other part of India, Rural population, Hindu religion and Squamous cell carcinoma occupies most common data in their categories.

The acute toxicity seen after Radiotherapy is mostly of Grade 2 skin reaction and mucositis which can be easily manageable.

In this study revealed that external radiotherapy with concomitant weekly carboplatin gave excellent response rate in carcinoma cervix, in comparison with external radiation alone.

In a study held at Department of Obstetric and Gynecology, University of Southern California school of Medicine, Los Angeles, USA, they evaluated carboplatin is a radio sensitizer in advanced cervical cancer. Standard radiotherapy techniques were used to treat patients with Stage IIA-IIIB cervical cancer. Intravenous carboplatin was administered twice weekly concurrent with external beam radiation. Of 22 evaluable patients, there were 19 complete responders of whom 15 remain alive: 11 patients were alive and disease free at last visit for a median duration of 15 months follow-up (range, 4-43 months) and 4 patients remain alive with disease for a median duration of 17 months (range, 3-55 months). Seven have died, one of whom was without evidence of disease. There were no treatment-related deaths and no grade 4 toxicity. The most significant adverse effect was hematologic resulting in four patients with grade 3 neutropenia or anemia. There were no fistulae or late gastrointestinal or genitourinary complications.^[7-9]

An another study done by Instituto Nacional de cancerologia, Mexico, Micheletti et al. reported a phase I-II study of radiation plus continuous infusion of carboplatin in 12 patients with stages IIB and IIIB cervical cancer, using 12 mg/m/day for a total dose of 504 mgm in 42 days, equivalent to 250 mg/m every 21 days for two courses. This schedule

proved well-tolerated and effective, leukopenia grade 2 the most frequent toxicity and complete response was observed in 75% of patients. Interestingly, patient pharmacokinetic studies showed that the platinum steady-stated in both plasma and tumour cells was not achieved and was below the concentration required in vitro to produce radio-potential, these results suggested that the optimum dose of carboplatin must be higher. In another report on carboplatin as radiosensitizer, 22 patients staged from IIA-IIIB were treated with 30 mg/m twice a week with escalation at 40 mg/m and 50 mg/m²; however, after several patients were treated the dose was re-calculated according to area under the curve (AUC). Accordingly, the authors suggest that an AUC of 6 could be adequate on the basis that only two of nine patients presented leukopenia grade 3. In a phase I study of weekly carboplatin during radiation, 24 FIGO stage IIIB patients were treated with standard pelvic radiation concurrently with six weekly applications of carboplatin at the following dose levels: I (100 mg/m); II (116 mg/m); III (133 mg/m²), and IV (150 mg/m). Six patients per level were treated, and all but two completed external beam and intracavitary treatment. The treatment was well tolerated, median number of weekly applications of carboplatin was six, and dose-limiting toxicity (leukopenia and/or neutropenia) was present in 50% of patients treated at the higher-dose level (150 mg/m), whereas this occurred in 33% of patients at 133 mg/m; hence, this dose was that recommended for use in further trials. Remarkably, the clinical response rate was similar to that reported for standard cisplatin. The treatment of locally advanced cervical cancer.^[10-14]

Another study done by department of Radiation Oncology, Carolinas Medical Centre, Charlotte, NC 28203, USA on June 2003 was concurrent carboplatin with pelvic radiation therapy in primary treatment of cervix cancer. Thirty-one evaluable patients were enrolled. The majority of patients had early stage disease. Carboplatin was successfully administered in 175 out of 186 (94%) planned treatments. All patients completed the prescribed course of radiation therapy. The mean treatment time was 50 days (36-73). There were no treatment delays for neutropenia or gastrointestinal toxicity. No patient was hospitalized for treatment related toxicities. Gastrointestinal toxicity equivalent to grade 3 or 4 was not reported. The objective tumor response based on physical exam findings and computed tomography measurements was 90%.^[15-18]

CONCLUSION

On the basis of study concluded that Patients with cervix cancer can be treated on schedule with concurrent carboplatin with EBRT. This regimen is well tolerated and produces excellent response rates and acceptable toxicities.

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