

A COMPARATIVE STUDY OF CONCOMITANT CHEMO-IRRADIATION WITH MITIMYCIN –C & FFU VERSUS CONVENTIONAL RADIOTHERAPY ALONE IN ADVANCED CASES (IIB – IV A) OF CARCINOMA OF UTERINE CERVIX

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Abstract:

Background- Over the years, improvements in radiotherapy techniques, the result of treatment in advanced cases of Ca Cx (carcinoma uterine cervix) have not changed and remains between 30 – 40 % in the best of centers. In order to achieve better response rate and survival, various techniques have been used including radio-sensitizers, hyperbaric oxygen, altered fractionation schedules, concomitant chemoirradiation and combined surgery and radiotherapy.

Patients and methods- A clinical study using conventional radiation 2 Gy / fractions / 5 fractions per week in one arm and concomitant chemoirradiation with Mitomycin C (MMC) & 5 Fluorouracil (FFU) in second arm was carried out in advanced cases of carcinoma of uterine cervix (IIB – IVA). The observations made were used to compare the response to treatment and complications/toxicities of the two types of treatments. At cancer hospital Jabalpur, we used conventional radiation in 100 cases of histological proven and clinically staged advanced squamous cell carcinoma of uterine cervix (Ca Cx). 50 cases received concomitant chemotherapy with MMC + FFU along with conventional radiation and 50 cases received radiation alone.

Results – In this study of 100 patients, it was observed that concurrent chemoirradiation was associated with acceptable toxicities. Complete response to treatment was better in chemoirradiation arm 63.3% as compared to 45.4% in conventional radiotherapy alone.

Key Words – Conventional Radiotherapy, Chemoirradiation, Advanced Cancer Cervix

Introduction

Cervical cancer is the commonest cause of death among women in developing countries¹. A study on cervical cancer prepared by national institute of cancer prevention and research (NICPR) reveals, India accounts for 1/4 of global burden of cervical cancer. It accounts for 17 % of all cancer deaths among women aged between 30 – 69 yrs. Cervical cancer, mainly caused by Human Papilloma virus, is leading cancer in Indian women and 2nd most common cancer in women worldwide².

All the deaths due to cervical cancer is also an indicator of health inequalities³, as 86% of all deaths due to cervical cancer are in developing, low and middle income countries⁴.

For years radiotherapy has been the primary modality of treatment for advanced stage of Ca Cx (II – IVA) either used alone or in combination with surgery and chemotherapy. Over the last few years, Significant improvements have been made in the techniques of radiotherapy, both external beam and brachytherapy. Despite

this improvement, the results of treatment have not changed much and remain between 30 – 40% in the best of the centers. Several techniques have been developed to achieve better response rates and survival and they include radio-sensitizers, hyperbaric oxygen, altered fractionation schedules and combined surgery and radiotherapy.

With the aim to improve the results of treatments in advanced stage Ca Cx, chemotherapeutic agents also have been used for last 2 -3 decades. It is being used in various forms and modality viz. neo-adjuvant, concomitant or adjuvant. But only concurrent chemoradiation with cisplatin and other agents like FFU^{5,6,7} have recently been proven to give better response rates, disease free survival and overall survival in carcinoma cervix.

In case of carcinoma of uterine cervix, majority of studies in 1980-1990 explored concomitant chemoradiation with chemo-therapeutic agents like FFU and MMC. Early studies of this combination employing several doses and scheme of FFU & MMC were small and included patients with either advanced or recurrent disease. Results were reported as encouraging with good local control and tolerable side effects^{10,11,12}

At Cancer hospital, NSCB Medical College, Jabalpur Feb 1999 – May 2000, we used conventional radiation along with hypoxic cell radio-sensitizer MMC and FFU and compared the results with conventional radiotherapy⁸.

Aims & Objectives

The study was used to compare chemoradiation with conventional radiation with respect to –

1. Tumour regression and loco-regional response.
2. Disease free period following treatment
3. Toxicities
4. Economic viability

Material And Methods

Eligible patient were previously untreated, histological proven advanced squamous cell carcinoma of Ca Cx (II B – IV A). The patients were assigned to two groups comprising 50 patients each. Prior to treatment all patient underwent complete history and physical examination and laboratory evaluation including complete haemogram, urea and

Creatinine. Radiological evaluation included X – ray chest PA view, Ultrasound Abdomen and other investigations as and when indicated.

Both group received conventional radiation. 2 Gy / Fr / 5 Fr / week through parallel opposed pair of AP – PA portals on a cobalt teletherapy unit. The total dose range was 60 – 70 Gy in 6 – 7 weeks. The initial field was treated to 50 Gy followed by reduced field boosts of 10 - 20 Gy. Chemotherapy in chemoradiation group consisted of IV single bolus Inj. MMC 6 mg / m² as per body surface area on day 1 and two courses of short day infusions on Inj. FFU 15 mg / kg body weight dissolved in 5% dextrose and infused over 3 – 4 hours on day 2 – 4 and day 22 – 24 of radiation. Patient were clinically assessed for response at 30, 40, 50, and 60 Gy while on treatment and then monthly after completion of treatment. The clinical assessment on first monthly visit was recorded as the response, i.e. – complete, partial, no response or progression. Complete response was defined as complete resolution of all abnormality ascribable to tumour on pelvic examination. A partial response was defined as at least 50% decrease in the tumour size as determined on pelvic examination.

Results

Comparative characteristics of patient in the two groups

Table – 1

Parameters		RT Alone	Chemo RT
		Case No.	Case No.
Age Range 26 – 65 Yrs		Majority 30 -60 Yrs	Majority 30 – 60 Yrs
Residence	Urban	11	11
	Rural	39	39
Literacy	Literate	12	13
	Illiterate	38	37
Socio-Econo.	Low	36	34
	Middle	14	15
	Higher	00	01
Symptoms	Bleeding PV	43	43
	Dicharge PV	25	37
	Pain ABD.	08	05
HPR	Well Diff.	04	04
	Mode. Diff.	29	24
	Mode. Diff.	29	24
	Poorly Diff.	17	22
Clinical Stage	IIB	30	34
	IIIA	03	02
	IIIB	17	12
	IVA	00	02

It is very obvious from the above table that the incidence of Ca Cx is most common between the age of 30 – 60 yrs. The incidence of Ca Cx is almost 3.5 times common in rural population. The incidence of Ca Cx is almost 3 times higher in illiterate population.

In our study 70% cases of Ca Cx are seen in lower socio-economic status. 29% in middle class and only 1% is seen in higher socio-economic status.

Table – 2
Response According To Figo Clinical Status⁹

Stage	Conventional			Chemoirradiation		
	Total Cases	CR	PR	Total Cases	CR	PR
IIB	26	14	12	32	20	12
IIIA	03	01	02	01	01	-
IIIB	15	5	10	10	07	03
IVA	-	-	-	01	00	01
Total	44	20	24	44	28	16

12 patients 6 from each group discontinued the treatment and did not come back. All patients had an objective response to treatment. The complete response (CR) in chemoirradiation arm was 63.3% as compared to 45.4% in conventional arm. Partial response (PR) was 36.36% in chemoirradiation arm and 54.54% in conventional arm.

Toxicities
Patients with grade II toxicity

Toxicity Type	RT Alone	Chemo RT
Vomitting	8	4
Diarrohoea	20	14
Genito-Urinary	10	22
Rectal	7	3

Table – 4
Patients with grade III toxicity

Toxicity Type	RT Alone	Chemo RT
Diarrohoea	1	3
Genito-Urinary	0	1

The haematological toxicity manifested in the form of anaemia and number of cases that develop anaemia attributable to treatment is depicted in table – 5. None of the patients develop leucopenia or thrombocytopenia.

Table – 5
Anaemia

Anamia HB < 10 GM%	On Presentattion	On Discjcharge
Radiotherapy Alone	31	40
Chemo RT	27	41

Table – 6
Distribution Of Late Toxicity

	Pigmentation	Fibrosis	Fistula	Stricture
RT Alone	3	4	1	1
Chemo RT	1	3	-	-

Table - 7
Reoccurrence On Follow –Up

Group	Stage	No. Of Roccurrence		
		< 4 months	4 – 8 months	9 -12 months
RT Alone				
CR - 20	IIB	1	5	0
	IIIA	0	1	0
	IIIB	0	2	0
Chemo RT				
CR – 28	IIB	1	2	0
	IIIA	0	0	0
	IIIB	0	0	2

The percentage of reoccurrence in radiotherapy alone was 45%; i.e. 9 out of complete responders (CR), whereas the percentage of reoccurrence within 12 months of treatment completion in chemoirradiation was only 17.85% (5 out of 28 cases)

Table – 8
Distribution Of Reoccurrence – Loco-Regional vs Distant

Group	Loco-Regional	Distant
RT Alone	8	1
Chemo RT	4	1

Treatment related toxicities are well tolerated in both the arm and there was no incidence of treatment delay or grade IV toxicity.

Discussion

It has become evident that chemotherapy and radiation therapy alone are unable to produce prolong disease free survival in patients with advanced stage carcinoma cervix. Theoretically, primary treatment of advanced Ca Cx consists of various forms of combined radiotherapy and chemotherapy. It has the advantage of direct anti –tumour effects of the two treatments and interaction of sensitizing properties of cytotoxic agents with radiation.

We conducted this study to evaluate the feasibility and tolerability of concomitant chemoirradiation in our clinical setting, where patients usually report very late with poor

socio-economic and illiteracy and are from rural population and mostly are anaemic. Keeping all this on the back of our mind we need to have a treatment option which is economically viable (since FFU and MMC are cheaper cancer drugs), patients friendly and all the protocol to be under supervision (indoor chemotherapy schedule) of a trained nursing staff and therefore we chose FFU and MMC as an agent for our study in concomitant chemoirradiation group.

In view of the consistency and extent of survival benefits when concomitant chemoirradiation was given, the acute toxicities observed are more but were manageable. The long term toxicities need to be evaluated further¹³. Cutaneous toxicity and gastrointestinal toxicity were the principle adverse effects in our study in patients who are in concomitant chemoirradiation group.

Our regimen was chosen with both combined cytotoxicity and sensitizing objectives in mind. Our data suggest that the combination of MMC and FFU in the doses administered is easily tolerated. While our initial responses are optimistic, we feel that more extensive experience with concomitant chemoirradiation is required with optimal use of radiotherapy techniques that include brachytherapy and interstitial implants.

Summary And Conclusion

1. Better complete responders (CR) seen in patients who are in chemoirradiation group.
2. Women from poor socio-economic status, who are uneducated and from a rural background present with more advanced stages of Ca Cx.
3. Anaemia is a common pretreatment finding seen in all patients in both study groups.
4. In view of point 2 mentioned above, treatments for advanced Ca Cx should be more affordable which we envisaged in our study.
5. Routine practice of performing Pap smear in any women above 35 years of age should be done at the level of primary health centres so as to reduce the overall incidence of Ca Cx and associated mortality.

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