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TO FIND OUT THE TOXICITY PROFILE OF TWICE WEEKLY CISPLATIN OVER CONVENTIONAL ONCE WEEKLY CISPLATIN BASED CRT IN LOCALLY ADVANCED CERVICAL CANCER.

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Abstract
Background: Carcinoma cervix ranks fourth most common malignancy (for both incidence & mortality) globally and third most common diagnosed malignancy in females (~16.5%) in India, (after breast & lip/oral cavity), with about 80% of the total burden occurring in developing countries like India.
Methods: This Prospective comparative study was conducted in the Department of Radiotherapy and Oncology TCC, IGMC, Shimla, in patients suffering from
advanced carcinoma of cervix.
Results: Hematological toxicities were seen mainly in the study group as compared to the control group (28 patients in the study group vs. 22 patients in control group). The difference was not statistically significant (p = 0.214). Grade III toxicities were seen in 5 patients in study group and 4 patients in control group. Cutaneous toxicity of different grades was seen in all the patients in the study arm and of the patients in the control arm. There was no statistically significant difference between the two arms (p=0.8121).
Conclusion: Both (Study & control) groups are comparable in terms of toxicity and are equally well tolerated by the patients.
Keywords: Chemoradiotherapy, RT, Partial response, toxicity.

Introduction

Carcinoma cervix ranks fourth most common malignancy (for both incidence & mortality) globally and third most common diagnosed malignancy in females (~16.5%) in India, (after breast & lip/oral cavity), with about 80% of the total burden occurring in developing countries like India.[1]

In recent times the most significant development in the treatment of carcinoma cervix has been the introduction of chemo therapy (based on cisplatin) to Radiotherapy. Chemotherapy used concomitantly with radiotherapy (CRT) has been investigated in many studies which have shown significant benefits in both survival and disease control. On the basis of these positive results, the National Cancer Institute strongly recommended the CRT as the standard treatment for patients with uterine cervical cancer in 1999.[2-5]

In the Asian countries due to differences in race, availability of radiotherapy facility, schedule and socioeconomic factors standardization of concurrent chemotherapy has not become possible. Thus different strategies also need to be conceived to enhance the effects of RT in suchsituations.

MATERIAL AND MEHODS

This Prospective comparative study was conducted in the Department of Radiotherapy and Oncology TCC, IGMC, Shimla, in patients suffering from advanced carcinoma of cervix.

Signed informed consent was taken from all patients involved in the study prior to enrolment in the study.

CASES INCLUDED

Cases included in this study were

1. Staged by FIGO staging 2008, stage II & III A, B

2. Histological proven - Squamous cell carcinoma,

- Adenocacinoma and

- Adenosquamous carcinoma.

PRE-TREATMENT WORK-UP:

Each patient enrolled in study underwent complete physical examination, including pelvic examination (under anaesthesia if needed) for clinical staging. Other investigations included complete haemogram, blood biochemistry, urine routine & microscopic examination, chest X-ray (P-A view), ultrasound abdomen & pelvis, & CT-Scan abdomen and pelvis. To exclude the bladder involvement urine cytology, cystoscopy, or Intravenous pyelography was done if needed.

EXCLUSION CRITERIAS:

The following category of patients were excluded

1. Stage – IA, IB and IV A, IVB.
2. Age >65yrs and <18yrs.
3. Histology other than squamous cell, Adenocacinoma or Adenosquamous carcinoma.
4. Patients who had prior pelvic surgery for cancer, pelvic radiotherapy or prior chemotherapy within 5 years.
5. Deranged KFT (BUN or creatinine 2 times above the normal limit).
6. Deranged LFT (Bilirubin 2 times above the normal limit),
7. Karnofsky performance status < or equal to 60,
8. Distant metastasis (disease beyond true pelvis).

STUDY DESIGN

CONTROL ARM: Patient was subjected to standard cisplatin based chemotherapy given concurrently with radiotherapy on the first day of treatment week (~1hour prior to radiation fraction).

Radiation

EBRT:-

Dose per fraction was 2Gy

Total dose: 50 Gy in 5 weeks. (5# /week).

Chemotherapy: Injection cisplatin 40 mg/m2 on D1 of every week, given ~1 hr. prior to radiation fraction.(with maximum ceiling of 60 mg / week).

Study arm: Patient were subjected to injection cisplatin 25mg per sqm on day 1 and day 4 every treatment week (depending on tolerability of patients).

Radiation

EBRT: Dose per fractionwas 2Gy

Total dose: 50 Gy in 5 weeks. (5# /wk)

Chemotherapy:

Injection Cisplatin 25 mg per sqm. Given i.v. on D1 and D4 every treatment week (depending upon tolerability).

Intracavitary Brachytherapy(ICBT) :- After a gap of 2 to 3 weeks of completion of EBRT, patients in both the arms were reassessed for response and patient were subjected to ICBT using Selectron remote controlled HDR system, Ir192based, giving a dose of 30 Gy (2Gy equivalent) to point A.

If they were not fit for ICBT the patients have been subjected to supplement

CRT

Supplement radiation therapy

CONTROL ARM - 20 Gy was given in 10 fractions @ 2 Gy / # over two weeks with inj. cisplatin (@40 mg /m 2) weekly.

STUDY ARM - 20 Gray will be given in 10 fractions @ 2 Gy / # over two weeks with inj. cisplatin given twice weekly on D 1 and D4 of every treatment week.

CONTROL GROUP:

- Dose of 50 Gy was delivered in 5 wks in 25# @ 2 Gy per fraction.
- 5 fractions were administered per week.
- Weekly inj. Cisplatin was given if complete haemogram, liver function & kidney function tests were found to be within normal limits.
- Radiotherapy fraction was delivered after ~1 hr. of inj.cisplatin@ (40mg/m2) on D1 of every treatment week & without chemotherapy on D2-D5 every treatment week.
- Mannitol containing formulations were preferred, if not available, diuresis was achieved with inj. Mannitol, post chemotherapy.
- Anti-emetic like 5-HT3 antagonists (palanosetron 0.25mg), was given 30 minutes before chemotherapy.
- Inj. cisplatin infusion was given over 90-120 minutes with adequate hydration.
- After 2-3 weeks of completion of EBRT, ICBT with (Ir- 192) HDR system was given @ 7Gy in 3 sessions one week apart.
- If patient was not found fit for the same, then supplement EBRT was given in the dose of 20 Gy in 2 wks & 10# @ 2Gy/# with inj. cisplatin 40mg/m2 weekly (with same ceiling as decided previousely).

STUDY GROUP:

- Total dose 50 Gy was given in 25 #s in 5 weeks @ 2 Gy/ # with concurrent cisplatin@25mg/m2 administered on D1 & D4 of every treatment week if

results of blood investigations (CHG, biochemistry) were WNL.

- 5 fractions were delivered per week.
- After 2-3 weeks of completion of EBRT patients were assessed for ICBT.
- Those fit were given ICBT with HDR system using Ir-192.
- If not found fit for ICBT they were subjected to supplement chemo radiation therapy. 20 Gy were given in 10 fractions @ 2Gy/# as 5fractions per week over 2 weeks.

Follow up:-

First follow up was done at six weeks of therapy. A complete gynaecological examination accompanied with systemic examination was performed and subsequent follow-ups done at every two months intervals. Patients examined locally and for any acute and late toxicity. Late toxicities were graded according to RTOG criteria.*

Secondary treatment

Patients who were having persistent tumor on completion of treatment were considered for salvage surgery if resectable. Adjuvant chemotherapy was administered in patients with un-resectable disease.

STATISTICAL ANALYSIS:-

Response rate was the primary end point for analysis. The various prognostic factors effecting response were also analysed. The data obtained from both arms was analysed by student "t"-test and chi-square test and p value of < 0.05 was taken as significant.

The statistical significance will be defined as:

- p> 0.05 non-significant
- p 0.05 – 0.01 significant
- p< 0.01 highly significant

RESULTS

Table 1: HEMATOLOGICAL TOXICITIES (STUDY VS. CONTROL ARM)

Hematological toxicities	Study arm		Control arm	
	No	Percentage	No	Percentage
Grade 1	6	21.00	5	18.00
Grade II	6	21.00	6	20.00
Grade III	5	19.00	4	12.00
No toxicities	11	39.00	15	50.00
Total	28		30	

Hematological toxicities were seen mainly in the study group as compared to the control group (28 patients in the study group vs. 22 patients in control group). The difference was not statistically significant (p = 0.214). Grade III toxicities were seen in 5 patients in study group and 4 patients in control group.

Table 2: CUTANEOUS TOXICITY (STUDY VS. CONTROL ARM)

Cutaneous toxicities	Study arm		Control arm	
	No	Percentage	No	Percentage
Grade 1	12	44.00	17	57.00
Grade II	14	50.00	11	36.00
Grade III	2	6.00	2	7.00
Grade IV	0	0.00	0	0.00
No toxicities	0	0.00	0	0.00
Total	28		30	

Cutaneous toxicity of different grades was seen in all the patients in the study arm and of the patients in the control arm. There was no statistically significant difference between the two arms (p=0.8121).

Table 3: GASTROINTESTINAL TOXICITY (STUDY VS. CONTROL ARM)

GI toxicities	Study arm		Control arm	
	No	Percentage	No	Percentage
Grade 1	12	44.00	18	60.00
Grade II	12	14.00	8	27.00
Grade III	4	14.00	4	13.5
Grade IV	0	0.00	0	0.00
Grade V	0	0.00	0	0.00
Total	28		30	

All patients in the study arm and in the control arm suffered gastrointestinal toxicities. Grade II GIT toxicity (upper/lower) were seen in 42% of the patients in study group, 43% in control arm. The difference was not statistically significant (p=0.762). Though Grade 1 toxicities were observed more in control arm as compared to study arm (60% vs 44.44%).

Two patients had experienced renal toxicity in the control arm and patient in the study arm which was not statistically significant (p=0.631)

There was not much difference between the two arms in genitourinary toxicity with 9 incidents in STUDY arm and 7 in the CRT arm both of grade 1. The difference being non significant (p = 0.789).

DISCUSSION

Despite the reduction in the incidence of cervical malignancy in western world it still remains the leading cause of female malignancy in the developing world.

Recent times have witnessed the introduction of chemotherapy in the treatment of this disease. Its

use in the concurrent setting with radiation has led to improved treatment outcomes. The NCI alert in 1999 heralded concurrent chemoradiation becoming the standard treatment especially in the developed countries as compared to developing countries, where in several problems of cost, medical problems like nephrotoxicity, elderly age group, poor general condition, refusal of the patient etc preclude its administration.

Overall, hematotoxicity was seen mainly in the study group 62.2% as compared to the control group 48.8%.These findings were comparable with the study by(by L.C. Wong, Y.C. Choo, D Choy et al)[6]. Grade 3 toxicity was seen in 9 patients in study arm and 6 patients in control arm. In 5 patients chemotherapy had to be deferred for one cycle in study arm and in 3 patients in control arm. While in others a delay of 2-3 days in subsequent cycle was seen. The difference was not statistically significant (p = 0.541).

Thus hematotoxicity was mainly encountered in the study arm but it was managed consrvatively

Grade II cutaneous toxicities were seen more in Study arm as compared to control arm (65.55% vs 53.33%)but it was no statistically significant (p= 0.0613) whereas Grade I toxicity was seen more commonly in Control arm which was not statistically significant.

The gastrointestinal toxicity of the study arm was Grade III in 7.8 % of the patients, compared to 6.6% in the control arm but the difference was not statistically significant. This was encountered mainly in the third and fourth weeks in the study arm and fourth and fifth weeks in the control arm.

The control group had also shown gastrointestinal toxicity and this was expected. The recent Cochrane review29 also shows a significant increase in serious GI toxicity for the groups of trials using platinum-based chemoradiotherapy.

On the basis of this data we can say that the treatment in the form of twice a week during radiation therapy is feasible in patients with locally advanced carcinoma of the cervix without excessive morbidity.

CONCLUSSION

Both (Study & control) groups are comparable in terms of toxicity and are equally well tolerated by the patients.

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