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Study of Weekly Paclitaxel with Concurrent Radiotherapy V/S Weekly Cisplatin with Concurrent Radiotherapy in Advanced Cervix Carcinoma

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Results: At end of the completion of treatment 76% in the study group and 72% in the control group were found to have complete response to the treatment, 16% and 20% were found to have partial response in the study and control group respectively.statistical analysis was done by chi Square test. After 6 months of completing the treatment the result were equivalent in both the groups, 84% had complete response and 8% had partial response. Though the difference in tumour response was not statistically significant(χ^2 = .13, p = 0..94)., the rate of reduction in tumor size was found faster in study group at the end of the treatment, complete response was little more in the study group. The vomiting during the treatment is statistically significantly more in the control group(χ^2=23.548,p=<0.0001).Total leukocyte count was significantly decreased more in study group compared to control group.(χ^2=9.8,p=0.0106).

Conclusions: The overall response with the use of paclitaxel, which is the study arm, are equal to those with cisplatin. Though not significant, but tumor response was more in paclitaxel arm compared to cisplatin arm.

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I. Introduction

Cancer is the third biggest killer in India. India recorded 9.8 lakh new cases of cancer in the year 2010, an increase of about 80,000 new cases as compared to 2009. *I*n India, four lakhs die of cancer every year. There is data that shows 25 lakh cancer patients in the country at any point in time. By 2015, the number of new cases in India is expected to cross 15 lakhs(1). Among Indian males, lung, head and neck cancer is the most common and among women, breast and cervical cancer is the most frequent. Carcinoma of the Uterine Cervix is the most common malignancy to affect females of developing countries. It ranks second in incidence among females, after Cancer Breast. Worldwide, approximately 5 lakh new cases are identified each year and about 2.33 lakh patients die of the disease (2). In developing countries, it accounts for about 3.4 lakh new cases & 1.6 lakh deaths every year (3).In India about 1.82 lakh new cases & 80,000 deaths every year from this disease (4).An estimated 1,82,027 new cases and 77,096 deaths due to cervical cancer occurred in India in 2010, contributing to 29% and 30% of the global burden of cervical cancer incidence and mortality(5).

Patients with Cervical Cancer usually present with locally advanced disease that is clinically confined to the pelvis (FIGO stage IIB, III & IV) in which surgery has higher morbidity. Radiotherapy plays a major role in management of these patients. The limitation of radiotherapy in controlling pelvic diseases for locally advanced cervical cancers is that radiation doses required to treat large tumours in the setting of poor tumour oxygenation exceeds the limit of toxicity in normal tissue. This was the main reason for treatment failure supporting by the fact that about 70% of relapses have pelvic failure as the first sites (6). Many strategies have been made trying to improve outcomes in locally advanced diseases such as uses of hypoxic cell sensitizers, hyperbaric oxygen, neutron therapy, and hyper-fractionation. However, results of those mentioned were found limited or unsuccessful (7). After a 1999

National Cancer Institute (NCI) Clinical alert was issued, chemoradiotherapy has become widely used in treating women with cervical cancer . Cisplatin is considered the most active cytotoxic agent and the drug of choice for concurrent chemoradiation. Meta-analysis studies have also demonstrated improved local control rates and survival with cisplatin-based chemotherapy concurrent to radiation therapy (RT). Although many prospective studies had shown that CTRT with cisplatin-based chemotherapy clearly improve the outcome of patients with carcinoma of the cervix, many patients treated on these protocols continue to fail in the pelvis and at distant sites [8]. In addition, one intergroup study using weekly concurrent cisplatin with radiotherapy for patients with carcinoma of the cervix could not demonstrate a beneficial effect of CTRT over standard RT alone [9]. This non-superiority finding was attributed to many factors like possible enrollment of patients with paraaortic lymph nodes, and an imbalance among randomization groups for known prognostic factors such as anemia [10]. These facts have lead many groups to investigate other drugs for CTRT like paclitaxel in an attempt to improve on what can be achieved by concurrent cisplatin [11].Paclitaxel is a taxane chemotherapy drug that was found to have significant activity in solid tumors especially epithelial ovarian cancer, lung, and breast cancer . Preclinical studies have shown a radiosensitizing effect of paclitaxel in human cervical cancer cell lines.(12)

At Our Centre, the treatment for locally advanced cervical cancer is concurrent chemoradiotherapy; the protocol is cisplatin 50 mg/m2 once a week for 5 weeks concurrent with pelvic radiation . Radiation is administered with cobalt-60 and HDR Brachytherapy. Paclitaxel is also radiosensitizing agent ,We conducted study to investigate the efficacy and response of Paclitaxel with concurrent radiotherapy versus Cisplatin with concurrent radiotherapy.

II. Method and Meterials

Patients coming to the department of radiotherapy & cancer treatment centre, SMS medical college &hospital jaipur were included in the study.After proper evaluation of the Biochemical and Hematopoietic profile, 50 patients were randomly divided into study and control group.

III. Inclusion Criteria

1. Patients with newly diagnosed cases of Squamous Cell Carcinoma Cervix FIGO stage-III &IV were taken for study and control group.
2. Patients with advanced & inoperable cervix cancer.
3. Age between 18 to 70 years.
4. ECOG (eastern cooperetive oncology group) performance status. 0 to 2.

IV. Exclusion Criteria

1. Patients previously treated with radiotherapy ,Surgery, Chemotherapy.
2. Any histology other than squamous cell carcinoma.
3. Poor perfomence status ECOG 3 &4.
4. Any uncontrolled intercurrent illness.
5. Pt who don't give consent for the study.
6. Class III & IV cardiac failure according to NYHA classification.
7. Pregnant & lactating women.

In the study and control group , patients were given 5 weeks of external beam radiotherapy followed by brachytherapy. External beam irradiation each of 200cGy/fr, on linear acceleretor by parallel opposed – anterior and posterior fields was given. External beam irradiation was followed by Intracavitary brachytherapy 700cGy/week for 3 weeks each with High Dose Rate Iridium 192 source. Patients received 50 Gy by External beam irradiation (200cGy/fr, total 25 Fr) and 21 Gy by Intracavitary brachytherapy (7Gy/fr, 3fr) .In control group, patients were treated by concurrent weekly cisplatin with external beam radiotherapy.In study group patients were treated by concurrent weekly paclitaxel with external beam radiotherapy .

Response was assessed as per the RECIST Criteria 1.1(13) .The results of study group were analyzed & compared with control group in terms of various aspects like side effects, tumor response, & local disease status. The data thus collected were analyzed by using Chi-square test for co-relation.

V. Results

Treatment Response at The end of Study

Table a shows treatment response of disease of patients using RECIST version 1.1 criteria while on treatment and subsequent follow up.

After 2nd week of initiating treatment, 9 (36%) patients of study group and 8 (32%) patients of control group had partial response, 16 (64%) patients of study group and 17 (68%) patients of control group had stable disease ($\chi^2 = 0.089$, $p = 0.76$).

After 4th week of initiating treatment, 2(8%)patients of study group and 1(4%) patients of control had complete response, 18 (72%) patients of both study & control group had partial response and 5 (20%) patients of study group and 6 (24%) patients of control group had stable disease ($\chi^2 = .42$, $p = 0.80$).

After 5th week of initiating treatment, 4(16%) of control group and 5(20%) of study group had complete response, 17 (68%) patients of control group and study group had partial response 4(16%) patients of control group and 3 (12%) patients of study group had stable disease ($\chi^2 = .25$, $p = 0.88$).

At end of treatment,18(72%) of control & 19(76%) of study group had complete response, 5 (20%) patients of control group and 4(16%) patients of study group had partial response 2 (8%) patients of study group and control group had stable disease (χ^2 = .13, p = 0..94).

At 1st month of follow up, 19 (76%) patients of control group and 20 (80%) patients of study group had complete response 4 (16%) patients of control group and 3(12%) patients of study group had partial response and 2 (8%) patients of study group and control group had stable disease (χ^2 = .16, p = 0..91).

At 3rd month of follow up, 21 (84%) patients of study group and control group had complete response, 3 (12%) patients of study group and control group had partial response and 1 (4%) patients of study and control group had stable disease (χ^2 = 0, p = 1).

At 6th month of follow up, 21 (84%) patients of study group and control group had complete response, 4 (16%) patients of study group and control group had partial response and none patients of study group and control group had stable disease (χ^2 = 0.14, p = 0.699).

Table a : Treatment Response Evaluation For Disease Control

TREATMENT RESPONSE	STUDY GROUP					CONTROL GROUP					STATISTICS	
	Complete Response	Partial Response	No Change	Progressive Disease	TOTAL	Complete Hesponse	Partial Response	No Change	Progressive Disease	TOTAL	χ^2	P

2nd week	0	9	16	0	25	0	8	17	0	25	0.008	0.76
4th week	2	18	5	0	25	1	18	6	0	25	0.042	0.80
5th week	5	17	3	0	25	4	17	4	0	25	0.025	0.88
End of Treatment	19	4	2	0	25	18	5	2	0	25	0.013	0.94
1st month	20	3	2	0	25	19	4	2	0	25	0.016	0.91
3rd month	21	3	1	0	25	21	3	1	0	25	0	1
6th month	21	4	0	0	25	21	4	0	0	25	0.014	0.699

Acute Toxicity During Treatment

The incidence of nausea during treatment in both the groups are summarised in the table b. As per RTOG criteria Table b shows that in the study group 10 (40%) of the patients had Grade 1 Reactions as compared to 6 (24%) in the control group whereas 2(8%) in the study group and 7 (28%) in the control group had Grade 2 Reaction and the incidence of Grade 3 was 2 (8%) and 5 (20%) in the study group and control group respectively(χ^2=5.9, p=0.11).

The vomiting during the treatment is statistically significantly more in the control group. 22(84%) patient in study group had Grade 0-1 vomitting and only 5(20%) had in study group, whereas only 3(12%) had grade 2-3

vomitting in study group, comparing to 11(44%) had grade 2 and 9(36%) had grade 3 vomitting in control group(χ^2=23.548,p= <0.0001).

The haematological toxicity is represented in the table b in three sub heads- haemoglobin, Total Leucocytes count and Absolute Neutrophil count. 4 (16%) and 5(20%) had grade 1, 21(84%) and 20(80%) had grade 2 heamoglobin level in the study group and the control group(p=1).

Total leucocyte count in the table b shows that study group had more grade 2 and 3 toxicity {6(24%) and4(16%)} comparing to control group having 2(8%) grade 2 toxicity &1(4%) having grade 3 toxicity. 8(32%) in study group and 19(76%) group had grade 0 toxicity, 7(28%) and 3(12%) had grade 1 toxicity in study and control group respectively. This difference is statistically significant, showing more toxicity in the study group compared to control group.(χ^2=9.8,p=0.0106), absolute neutrophil count shows the same pattern of toxicity profile. 10(40%) and 20(80%) had grade 0, 8(32%) and 3(12%) had grade 1, 4(16%) and 1(4%) had grade 2toxicity in the study and control group respectively. 3 (12%) developed grade 3 toxicity in the study group and 1(4%) in control group. This difference was statistically significant more in the study group compared to control group (χ^2=8.4,p=0.03).

There was no nephrotoxicity found in 24(96%) in study group and 19(76%) in the control group, while 1(4%) and 4(16%) were found to have grade 1 toxicity in the study and control group respectively and.1(4%) was found to have grade 2 toxicity in control group(p=.11)
Table b

VI. Discussion

The clinical feasibility of concurrent RT and paclitaxel was tested in phase I trials and a maximum tolerated dose (MTD) of 50 mg/m2 per week concurrently with radiation therapy was established . In addition, the clinical efficacy of paclitaxel has been tested in phase II and III studies for metastatic and recurrent cervical cancer with objective response rates ranging between 36 and 47% In all these studies paclitaxel was used in conjunction with either cisplatin (4/7 studies) or carboplatin (3/7 studies) but was never used alone for CTRT. The majority of these studies was phase I (4/7 studies), with one study being a combined phase I/II study conducted by the GOG [60]. The number of patients enrolled in these studies varied between 8 and 35 patients and the rates of progression free survival ranged between 39 and 88%. The dose limiting toxicity was primarily neutropenia in 4 studies [14,15] or diarrhea (14).

The present study was carried out on 50 histopathologically confirmed newly diagnosed cases of Squamous cell Carcinoma cervix Stage IB to IVA. These cases were registered for treatment in department of Radiotherapy at S.M.S hospital jaipur from December 2011 to June 2012.. In this study there was no statistically significant toxicity between the study group and control group for acute skin reaction, nausea during treatment, acute diarrhea, haemoglobin changes during treatment and nephrotoxicity. The statistically significant neutropenia was found in study group and vomiting in control group.

The tumour response in this study was evaluated in the 2nd, 4th, 5th week and at the end of treatment. After the completion, patients were evaluated every month til 6th month. Reduction in the tumour size was seen comparatively more in the study group and rendering them fit for brachytherapy earlier then the control group. In the 4th week of treatment 8% in the study group and 4% in the control group had complete response and in the 5th week 20% in the study group and 16% in the control group had complete response.

At end of the completion of treatment 76% in the study group and 72% in the control group were found to have complete response to the treatment, 16% and 20% were found to have partial response in the study and control group respectively. After 6 months of completing the treatment the result were equivalent in both the groups, 84% had complete response and 8% had partial response. Though the difference in tumour response was not statistically significant, the rate of reduction in tumour size was found faster in study group at the end of the treatment complete response was little more in the study group. So paclitaxel can be used as a radiosensitizer concurrently with radiotherapy in advanced inoperable patients in whom renal functions are not normal due to (1)hydronehrosis caused by advance disease,(2)Chronic renal disease.

VII. Conclusions

Our study provides a direct comparison between cisplatin and paclitaxel used as weekly concurrent chemotherapy with definitive radiation for advanced carcinoma of the cervix. Our data indicate that the overall response with the use of paclitaxel, which is the study arm, are equal to those with cisplatin. Though not significant, but tumor response was more in paclitaxel arm compared to cisplatin arm .However, the results were encouraging and it shall require larger number of patients and longer follow up in order to arrive at a concrete conclusion as far as disease free survival, cause specific survival, pelvic control rate, and long term sequel or complications are concerned.

VIII. Bibliography

1. Kounteya Sinha, TNN Nov 10, 2011, 04.40AM IST (TOI) Hoskins WC, Perez CA, Young RC, eds. Principles and practice of Gynecologic oncology, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.

2. Kvale G, Heuch I, Ursin G. Reproductive factor and risk of cancer of the uterine corpus: A prospective study. Cancer Res 48: 6217, 1988.
3. Sankaranarayanan R, Esmy PO, Raj Kumar Rand Muwonge R: Visual Screening and Cervical Cancer. The National Medical Journal of India. Volume – 20, Number 5, 370: 398 -406, 2007.
4. The Times of India 2012-10-21: Dr. Surendra S. Shastri Principles and Practice of Gynecologic Oncology, 4e Asian Pacific Journal of Cancer Prevention, Vol 11, 2010
5. 7.Asian Pacific Journal of Cancer Prevention, Vol 11, 2010.
6. Keys HM, Bundy BN, Stehman FB. et al. Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for Bulky stage IB cervical carcinoma. N Engl J Med. 1999; 340:1154–61.doi: 10.1056/NEJM199904153401503.
7. Pearcey R, Brundage M, Drouin P. et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol. 2002;20(4):96672doi:10.1200/JCO.20.4.966. 7.
8. Rose PG. Concurrent chemoradiation for locally advanced carcinoma of the cervix: where are we in 2006? Ann Oncol. 2006; 17(Suppl 10):x224–9. doi: 1093/annonc/mdl264.
9. Chen MD, Paley PJ, Potish RA. et al. Phase I trial of Taxol as radiation sensitizer with Cisplatin in advanced cervical cancer. Gynecol On-col. 1997; 67:131–6. doi:1006/gyno.1997.4851
10. DiSilvestro PA, Walker JL, Morrison A. et al. Gynecologic Oncology Group. Radiation therapy with concomitant paclitaxel and cisp-latin chemo-therapy in cervical carcinoma limited to the pelvis: a phase I/II study of the Gynecologic Oncology Group. Gynecol Oncol . 2006;103(3): 1038–42. doi: 1016/ j. ygyno. 2006.06.017.
11. New response evaluation criteria in solid tumours.