Concurrent Radiotherapy and Weekly Paclitaxel for Locally Advanced Squmous Cell Carcinoma of Uterine Cervix–Treated Patients at Rural Centre in India

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Abstract: ***This study was performed to analyze the efficacy and safety of con-current radiotherapy and weekly paclitaxel in the treatment of carcinoma of uterine cervix. Hundred patients with locally advanced (stages IIB to IVA according to FIGO classification) carcinoma of uterine cervix were enrolled, radiotherapy was conventionally administered: 50.4 Gy/28 fractions by external beam (whole pelvis) followed by HDR-Intracavitary brachytherapy, 4 fractions of 7 Gy each. Paclitaxel was administered on weekly basis at dose of 40 mg /m2 during entire course of external beam radiotherapy. Treatment response was evaluated three months after the end of radiotherapy by means of clinical examination and ultrasonography. Complete Regression (CR) in 83%, partial response (PR) 14% and progressive disease 3%. At 26 months of median follow up 73 patients alive, 58 patients are disease free. The results of this study suggest that concurrent chemo radiotherapy is feasible in treatment of carcinoma cervix with acceptable and manageable toxicity and paclitaxel act as radio sensitizer in locally advanced cervical cancer.***

Keywords: Paclitaxel, cervical carcinoma, HDR brachytherapy

1. Introduction

Invasive cervical cancer is the second most common malignancy in the women worldwide, after breast cancer, this account nearly 5, 00,000 new cases and 250000 deaths per year. [1]Of these, 80% occur in developing countries and 20% in developed countries.[2] The incidence rate in India among various cancer registries shows 17.2 to 30.7 per 100,000 women with highest incidence in Chennai, Brashi and lowest Incidence in Mumbai. The number of cervical cancer deaths in India is projected to increase 79000 by the Year 2010. In our department cancer cervix constitutes 25% of total cases seen.

Whereas, either radiotherapy (RT) or surgery represents the mainstay of treatment for patients with early stage cancer, while multimodality treatment strategies, including RT combine with cisplatin based chemotherapy (CT) or neoadjuvant chemotherapy or CT followed by radical surgery have been reported to improve disease free as well as overall survival. Concurrent Chemo radiation (CCRT) is established treatment modality in locally advanced cervical cancer.

In different sites, such as head & neck, lung, breast and brain tumors paclitaxel has been combined with radiation in phase I clinical studies. [3], [4] and [5] In phase II study on non-small cell lung cancer.[6]the maximum tolerated dose was 6omg/m^2/week; in these series an overall response rate (complete plus partial) was achieved in 84% of patients. Other studied demonstrated that combination of paclitaxel /cisplatin [7] and etoposide [8] in association with radiotherapy was a promising treatment for stage III non-small cell lung cancer.

In locally advanced cervical cancer, many phase I and II studied, paclitaxel alone or in combination with cisplatin, carboplatin in patients undergoing pelvic radiation therapy. This acts as radiosensitizer and synergistic action along with radiotherapy [9], [10]

CCRT is the established treatment modality in locally advanced carcinoma of uterine cervix. Many drugs like cisplstin, 5-fluorouracil and more recently paclitaxel are used as radiosensitizer. In addition to direct cytotoxic effect shows the theoretical advantage to sensitize malignant tissue to the effect of radiation. CT in facts may act synergisticacally with RT and inhibiting the repair of sub lethal damage along with promoting the synchronization of cells into a radiation sensitive phase of the cycle, and reducing the fraction of hypoxic cells resistant to radiation. Furthermore CT may independently increase the rate of death of tumor cells. In rural centre cervical cancer is leading malignancy and majority of patients presented with locally advanced staged. This prospective non randomized trial with 100 patients of locally advanced cervical carcinoma was conducted to analyze the efficacy and safety of con-current radiotherapy and weekly paclitaxel in the treatment of carcinoma of cervix, and this is the preliminary reports of our experience at a median follow up of 26 months.

2. Materials and Methods

During a period from July 2007 to June 2010, 100 patients of cervical carcinoma attending the department of Radiotherapy were included in prospective non randomized study of CCRT.

Eligibility Criteria were:

- No previous oncology treatment except biopsy.
- Histological/cytological diagnosis of cervical carcinoma.
- Age between 28-65years.
- HB >l0gm.
- Blood urea & creatinine not higher than twice normal value.
- ECOG performance scale score of 0-2.
- Informed consent oral and written from patients.
- ANC >2000, platelets >100000, bilirubin <1.5, serum creatnine, 1.5mg%.
- SGOT or SGPT <2 upper normal, creatinine clearance 50ml/min.
- No clinically significant medical problem like heart disease.
- No prior radiation therapy.

Patients characteristic are shows in [Table no. I]

3. Pretreatment Evaluation

- Detailed history and complete physical examination including bimanual pelvic examinations.
- Radiographic studies like X- ray pelvis, X-rays chest, USG abdomen and pelvis, if possible CT scan and MRI of pelvis also done.
- Laboratory studies including routine investigation like Hemoglobin estimation, total leukocyte count; differential count and platelet count; blood sugar and liver functions test, biochemical analysis.
- Clinical staging based on FIGO staging.

4. Treatment Designed

The treatment protocol schedule consisted of a course of RT combined with concomitant paclitaxel administered weekly during entire course of external RT.

Chemotherapy: Paclitaxel a dose of 40mg/m^2 was diluted in 100 ml of normal saline and administered by 30 minute infusion. Dexona 8 mg, Ranitidine 50 mg and Ondensetron 8 mg IV bolus, given30 min before paclitaxel.

Radiotherapy: All patients received RT to whole pelvis 50.4Gy ⁄ 28 fractions, one fraction per day, five days per week, with two parallel opposed pelvic fields A-P and P-A and four fields. Two fields technique were planned when inter portal distance (IPD) less than 20 cm. and four fields, when IPD was more than 20 cm. Last three fractions delivered using midline shielding, followed by HDR-Intracavitary brachytherapy (ICBT) 4 fractions of 7 Gy each (total 28 Gy) to reference point A (2 cm. superior and 2 cm lateral to the cervical Os) on twice weekly basis. Total dose to point A was 8360 cGy. Overall treatment time (OTT) was 50 days (range 49 to 52 days).

Evaluation of Follow-up: Before each course of CT patients were evaluated and during RT they were seen weekly by Radiation oncologist for normal tissue reaction and tumor response. Routine investigations were performed and if required supportive management was given. As per RTOG criteria adverse reaction was documented. During CT all patient were admitted in ward. Patients were examined after completion of RT and then at 6 weeks followed by 3 monthly bases up to two years than six monthly. Blood count, x-ray chest, USG abdomen. Patients belong to rural area were also motivated to come for regular follow up.

5. Response

After completion of treatment, all patients were evaluated for response and acute toxicity. Response was evaluated three months after the end of radiotherapy by means of clinical examination and USG. Complete regression (CR) was defined as disappearance of the disease according to both clinical and radiological examination. Partial regression (PR) was defined as tumor size regression more than 50%. A regression of less than 50% or stable disease (SD) was defined as no change (NC). Acute hematological toxicity was monitored weekly during treatment through serum examination and blood cell counts. Patient symptoms like diarrhoea, vomiting, dysuria were reported. Toxicity was scored according to WHO criteria.

6. Statistical methods

Patient characteristics, safety profile of the concurrent modality treatment administration, and response rates were characterized by descriptive methods. Locoregional relapse free survival (LRFS), Disease free survival (DFS) and overall survival (OS) curves were calculated according to the Kaplan- Meier method. For LRFS all local and /or regional recurrences and deaths due to disease were taken as events, for DFS all the deaths because of disease were taken as events, while for overall survival (OS) all deaths regardless of any cause were taken as events.

7. Results

All patients completed planned course of RT, there was no treatment related death or patients experienced severe reactions needs stop of treatment. Complete regression in 83 patients (83%), partial response in 14 patients (14%), while three patients had progressive disease (3%) stage wise response shown in [Table no. II]. Severe adverse effect during treatment-are mention in [Table No.III] while late radiation reaction mention in [Table No. IV]. After two years from last patents treated analysis done, only 73 patients on regular follow up, overall survival and disease free survival mention in [Table no. V], eight patients have locoreginal recurrences, three patients have liver metastasis, one patient have liver and lung metastasis, and two patients have bone metastasis. One patient has supraclavicular lymphadenopathy. Eight patients died during follow up and rest patients missed for follow up. Vaginal fibrosis developed in almost every patent, one patients developed rectovaginal fistula, two patients developed gross haematuria and eight patients developed rectal bleeding. Rectal bleeding cases were managed with steroid enema. Heamaturea cases were managed with symptomatically. Other recurrence cases were managed with either palliative radiotherapy or chemotherapy (cisplatinum & paclitaxel based). Our study is in preliminary stage only 26 months follow-up done, long

term follow-up is needed to derive response of treatment, recurrences and late complications. No cases of cardiac toxicity and alopecia were recorded.

8. Discussion

Definitive RT represents the standard treatment for locally advanced (FIGO stage IIB-IVA) squamous cell carcinoma of uterine cervix. RT is usually performed applying whole pelvic fields with a dose up to 50 Gy followed by boost with ICBT. Despite large tumor doses conventionally administered (65 Gy or more), failures are not uncommon. According to Perez [11] the actuarial highest probability of loco regional control after RT alone is 60% for stage III. On the other hand, achieving local CR after RT represent an important predictive factor of survival, being a 5 years survival rate of 76% when local CR is obtained, verses 41% when CR is not achieved[12]. The improvement of pelvic control cannot be reached by increasing radiation dose beyond the current levels without prohibitive morbidity. The consequences, in recent years, have been the development of chemo-radiotherapy regimens with which favorable results have been reported in tumor of other sites.

In locally advanced cervical carcinoma CCRT with cisplatin or cisplatin in combination with fluorouracil to external and ICBT improved the survival rate [13]. [14], [15] Paclitaxel was also used along with RT either alone or in combination with cisplatin or carboplatin by many workers [16], [17], [18], [19] and [20] shows that paclitaxel either alone or in combination with other agent act as radiosensitizer with good pelvic control. In our study shows that concurrent administration of paclitaxel at the weekly dose of 40 mg/m^2 and RT with conventional fractionation is feasible. The acute toxicity is not increased in respect to what is commonly observed during a conventional course of exclusive radiation treatment. In conclusion paclitaxel may be considered an effective radio sensitizer drugs. A complete response of 83% considered as satisfactory results.

Cerrotta M.D. et al. [16] randomized 20 patients with stage IIB-III advanced and recurrent cervical carcinoma evaluated for acute toxicity and response, RT was conventionally administered: 50.4Gy by external beam followed by intra-cavitary cesium or reduced transcutaneous field. Paclitaxel was administered weekly at the dose of 40 mg/m^2 or 60 mg/m^2 during entire course of external RT. CR was achieved 63% (12 patients). Five patients experienced grade III small bowel toxicity, one patient grade III bladder toxicity and one patient treated with 60 mg/m2 had grade IV mucositis. Out of 12 (CR) patients at the end of treatment, ten maintain complete local remission for a median follow up of 47 months but two had developed distant metastasis.

G.G. Rao et al (2005), [20] randomized 15 patients with new cases squamous cell carcinoma or adenocarcinoma of the uterine cervix of median age 44 Yrs, FIGO stage IB2 to IVA, negative Para-aortic lymph node and adequate organ functions were eligible. Pelvic RT (45Gy/5 weeks/1.8 Gy/ day, four fields) followed by two brachytherapy applications (point A LDR: 90 Gy, HDR: 75Gy). Concurrent weekly CT Paclitaxel 50 mg/m2 and Carboplatin AUC 1.5 for seven cycles administered during external radiotherapy. The results of this study show that MTD of Carboplatin is AUC 2.5 with Paclitaxel 50 mg/m^2. Median follow up is 17 month; three patients have recurred and two have died. The clinical CR was 80% and PR was 20%. The estimated 2 yrs PFS and OS 80% and 86%.

Me-Yeon Lee et. al. (2007), [18]:33 patients of cervical carcinoma (FIGO stage I to IVA) were treated with CCRT including two cycles of Paclitaxel 135 mg/m^2 and Carboplatin (AUC 4.5) at 4 weeks interval. All patients received external beam radiation therapy to the whole pelvis 41.4-51.4 Gy (median 50.4Gy) and high-dose rate brachytherapy 25.6- 43.3 Gy (median 34.6 Gy) and five patients with external beam radiotherapy with median 14.4 Gy. The CR was 70% and PR 30%. The 3 Years estimated disease free survival rates for stages I-IIA, IIB, III and IV were 89%, 91%, 88%, and 50% respectively.

Kim K et al. (2006), [19]: 37 patients with stages IB-IIB uterine cervical carcinoma were treated with radical hysterectomy and bilateral pelvic lymph node dissection followed by CCRT with two courses of Paclitaxel (135 mg/m^2) and Carboplatin (AUC 4.5 mg min /ml) at four week interval. All patients received external beam radiotherapy up to 50.4 Gy to the whole pelvis. Among these, 7 patients with close or involved resection margin received boost irradiation to vaginal cuff. Median dose of boost irradiation was 14.4 Gy. Acute toxicity was mainly hematological and gastrointestinal, mostly grades I and II. At median follow up of 27 month (range 10-46), all the patients achieved local control, and four patients experienced distant relapses.

OTT was 49-52 days (median 50days). To decrease OTT brachytherapy started after completion of external radiotherapy and two implants per week were done to 7Gy each of four implants. Many workers [21] [22]. Have been study effectiveness and safety of twice weekly HDR brachytherapy in cervical carcinoma. Shows that twice weekly HDR brachytherapy regimen may improve local control rate and decrease overall treatment time.

However some drawback was also present in this study.

1. It was not randomized.
2. Number of patient in less.
3. Study period in short
4. Follow up is poor.
5. Cause of death of patient is not known.

This study indicates that 5 courses of paclitaxel can be given as CCRT with manageable adverse effect in the management of locally advanced cervical carcinoma. However a large randomized study is needed to pin point if any. CT and RT controlled only tumor and tumor related death. It cannot improve the expected age; hence cause of death in every treated cancer patients should be evaluated.

Table 1: Patient's characteristics

Total No. of Patient	100	
Follow up (Median, Range)	37 Months (33to 57)	
Stage IIB	24	
Stage IIIB	62	
Stage IVA	14	
Age (Median, Range)	47.8 Years (28 to 65)	
Resident	Rural	70
	Urban	30
Degree of differentiations (SCC)	Moderately	48
	Well	28
	Poorly	24

Table 2: Over all response after completion of treatment

Response	*IIB*	*IIIB*	*IVA*	*Total*
CR	21	51	11	83
PR	2	9	3	14
SD	1	2	0	3
Total	24	62	14	100

Table 3: Acute reactions

Acute reaction	*Grade 0*	*I*	*II*	*III*	*IV*
Neutropaenia	84	13	3	0	0
Thrombocytopaenia	88	8	4	0	0
Hypersensitivity reaction	92	6	2	0	0
Nausea	20	38	52	0	0
Vomiting	26	52	22	0	0
Diarrohea	13	61	20	6	0
Urinary symptoms	40	54	6	0	0
Rectal symptoms	46	38	14	2	0

Table 4: Late reactions

Late reactions	*No. of cases*
Vaginal fibrosis	24
Rectovaginal fistula	1
Bleeding per rectal	8
Hematurea	2

Table 5: Follow-up after 2 years

Response	*Percentage*
Follow-up	73
DFS	58

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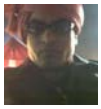
Author Profile



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