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A PILOT STUDY TO SEE THE FEASIBILITY, SAFETY AND EFFICACY OF CONCURRENT PACLITAXEL AND CISPLATIN IN PATIENTS OF LOCALLY ADVANCED CARCINOMA CERVIX, BEING TREATED WITH CONCURRENT CHEMO RADIATION

Radiotherapy

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ABSTRACT

Introduction: Carcinoma cervix, is the second most common cancer among Indian women (As per Globocon 2018). India alone accounts for one quarter of the world wide burden of carcinoma cervix. Cervical cancer is on declining trend in India according to the population based registries. The standard treatment for locally advanced (stage IIB to IVA) carcinoma cervix is cisplatin based chemo-radiation. **Aims:** This study is directed to evaluate the efficacy, feasibility of concurrent paclitaxel plus cisplatin in locally advanced carcinoma cervix, to assess tumour response at first follow up and subsequent follow ups by clinical examination and RECIST 1.1, and most importantly to evaluate the toxicity – according to RTOG (The Radiation Therapy Oncology Group) acute and chronic toxicity area. **Materials and method:** Single institutional, single arm, prospective, interventional, non-randomized, pilot study, among patients of locally advanced carcinoma cervix, similar to phase II trial revealing feasibility, efficacy and toxicity of proposed treatment. **Result:** During the treatment almost all patients needed blood transfusion for decrease in hemoglobin percentage from baseline. (Hematologic toxicity) 17 (56.7%), patient's peripheral blood picture had shown myelo-suppression of Grade II (low total leucosite count). But patients remained afebrile. Almost all the signs and symptoms disappear one week after completion of EBRT. Complete response(CR) – 28/30(93.3%) **Conclusion:** We conclude that, a concurrent chemo radiation regime Cisplatin (40mg /m2) with Paclitaxel (35mg /m2) produced satisfactory short-term efficacy with relatively tolerable acute toxicities and feasibility among women attending our institute.

KEYWORDS

Locally advanced Carcinoma Cervix, Cisplatin, Paclitaxel, Concurrent Chemo-radiotherapy, Efficacy and Toxicity.

INTRODUCTION

Cancer of the uterine cervix, or cervical cancer or carcinoma cervix, is the second most common cancer among Indian women (As per Globocon 2018). India alone accounts for one quarter of the world wide burden of cervical cancer. Cervical cancer is on declining trend in India according to the population based registries. The peak age of occurrence of cervical cancer in India is between 55 and 59 years and the highest age adjusted rates are in Aizawl in the north eastern part of India at 24.3 per 100,000 women[1]. Risk factors for the development of carcinoma of the cervix include HPV infection, age of first coitus, early age of marriage, poor genital hygiene, multiple number of sexual partners, oral contraceptive, malnutrition, HIV infection, low socio economic status, smoking etc. Especially due to lack of awareness and eventual screening, this potentially preventable malignancy poses a huge burden of disease. HPV infection prevalence rate is 87.8% - 96.67% among women with cervical cancer. There is evidence that cervical cancer incidence is greater among women of lower classes, those less educated, and those with a larger number of children. Women using oral contraceptive pills for more than five years are at an increased risk of developing cervical cancer[1].

FIGO Stage IIB2, III & IVA are the locally advanced carcinoma cervix. External beam radiotherapy with concomitant cisplatin as radio sensitiser given weekly 40mg/m2 one hour before EBRT, which is subsequently followed with brachytherapy is the standard mode of treatment[2]

Currently the value of adding cisplatin based chemotherapy to radiation for treatment of locally advanced cervical cancer is strongly supported by randomized studies and meta-analysis[3]. A strategy currently being investigated is the use of newer radiosensitizers alone or in combination with platinum compounds.

Alternatives to concurrent cisplatin based chemo-radiation, cisplatin has been combined with other cytotoxic agents and tried in patients with stages IIB to IVA cervical cancer, i.e. cisplatin & 5FU, cisplatin&gemcitabin, cisplatin& paclitaxel, etc.

Paclitaxel has been demonstrated to be a good radiosensitizer.

MATERIALS AND METHOD

Study Design: Single institutional, single arm, prospective, interventional, non-randomized, pilot study, among patients of locally advanced carcinoma cervix, similar to phase II trial revealing feasibility, efficacy and toxicity of proposed treatment.

Place Of Study: Department of Radiotherapy, I.P.G.M.E. & R. and S.S.K.M. Hospital, Kolkata, West Bengal, India.

Period Of Study: After the approval of the Ethical Committee of the institute (vide memo no. Inst/IEC/2018/074, Dated 20.01.2018) the selection and treatment of the patients was started from January 2018 and ended in May 2019.

Study Population: Patients suffering from histologically proved squamous cell carcinoma of cervix of stage IIB to IVA (FIGO 2018), attending the outpatient department of the institute.

Inclusion Criteria

1. Age – 18 to 65 years
2. HPE proven squamous cell carcinoma of cervix
3. Patients with stage IIB to stage IVA
4. ECOG performance status 0, 1, 2
5. No previous history of treatment of cancer
6. Creatinine clearance >or= 60ml/min
7. Patients must sign a study specific informed consent - written in her own language, prior to study entry

Exclusion Criteria

1. Histologically other than squamous cell carcinoma
2. Previous history of treatment for malignancy
3. Previous history of pelvic irradiation
4. Metastatic disease or other primary malignancy
5. Significant co-morbidities (eg. Diabetes, cardiac, hepatic or renal disease, AIDS etc.) that would not allow or would require modification of treatment of the study protocol

Sample Size: 30 patients

Sample Design: All patients diagnosed as locally advanced squamous cell carcinoma of cervix with ECOG status 0, 1, 2, aged 18 years to 65 years, without any significant co- morbidities. Single arm study, no control group is required.

Study Variables

i. Clinical stage at time of presentation IIB, III & IVA

ii. Age group
1. Up-to 40 years
2. 40 - 49 years
3. 50 – 59years
4. 60 years and above

iii. Socio-economic status by income
iv. Marital status- unmarried/married
v. parity- non-pregnant/single child/ two children/ >2children
vi. toxicity – skin toxicity, GI toxicity, haematological toxicity, renal toxicity

Treatment Protocol

After ethical clearance from the Institutional Ethics Committee (IEC), pre treatment data of patients was collected in case record form with history, detailed clinical examination, radiological assessment and laboratory investigation. CT scan with 3mm cut was performed from umbilicus to mid-thigh. CT scan images were brought to the treatment planning workstation (ONCENTRA). Contouring of GTV (gross tomour of cervix, vagina, para-metrium), CTV (probable area of microscopic disease), CTV lymph nodes (based on RTOG atlas), OARs (organ at risk), ITV (for movement of uterus & cervix due to differences in bowel and bladder filling), PTV (2-3 cm margin from CTV and/or ITV).

Usually AP-PA fields were used. When IFD (interfiled distance) was more than 20cm, 4field treatment was given.

EBRT (External Beam Radiation Therapy) was administered in Bhabatron II (Cobalt-60) treatment unit, in a dose of 50Gy (2Gy/fraction/day – 5fraction per week), with concurrent weekly injection paclitaxel (30mg/m2) plus injection cisplatin (40mg/m2). Both paclitaxel and cisplatin were transfused over 1hour, mixed with 500ml normal saline, along with proper pre-medication on Mondays. Chemotherapy was completed one hour before EBRT.

After completion of concurrent EBRT, patients were treated with intra-cavitory HDR Brachytherapy [Nucletron (Iridium-192) with Fletcher-Suite-Delclos applicator] – in a dose of 7Gy/fraction in 4fractions, 2fractions per week.

[Total biological effective dose to point A, 80-90Gy]

Objectives Of The Study

Response & toxicity assessment during treatment: patients were evaluated for acute toxicity, by daily physical examination (toxicity study and QOL questionnaire), and by weekly laboratory examination (complete blood count, urea, creatinine) on Monday during therapy. Data were graded according to the RTOG Acute Toxicity Criteria

Follow-up

Patients were assessed at 6week after completion of treatment by clinical examination (general and P/A, P/S, P/V), CBC, LFT, Urea, Creatinine, MRI with contrast of pelvis, and graded according to RECIST Criteria (version 1.1). If any suspected lesion was found, biopsy was taken.

Evaluation And Analysis

According to Response Evaluation Criteria in Solid Tumours (RECIST), short term efficacy was evaluated.

Briefly, disappearance of all target lesions with no new lesions appearing for >4weeks was considered a complete response (CR). A ≥50% decrease in target lesion volume with no new lesion appearing >4weeks was considered a partial response (PR). A decrease in target volume of <50%or an increase in target lesion volume of >25%, and appearance of new lesion volume of >25% was considered stable disease (SD). Finally, an increase in target lesion volume of >25% and the appearance of new lesion was considered progressive disease (PD). The sum of CR and PR cases divided by the total number of cases constituted the objective response rate (ORR).

Post treatment data from follow-up examination were recorded on case sheet. All the data was compiled. Statistical analysis was done to see the efficacy, feasibility and toxicity of the study.

RESULT

- The main outcome was acute toxicity (according to RTOG), and primary and or pelvic failure (RECIST 1.1).
- 4 (13.3%) patients had Grade IV skin toxicity, for which EBRT was temporarily stopped.
- Almost all patients needed blood transfusion for decrease in haemoglobin percentage from baseline. (hematologic toxicity)
- All patients experienced weakness and had reduced appetite during EBRT.
- 8 (26.7%) patients were admitted for management of diarrhoea.
- 17 (56.7%) patient's peripheral blood picture had shown myelosuppression of Grade II (low total leucosite count)
- Almost all the signs and symptoms disappear one week after completion of EBRT.
- Complete response(CR) – 28/30(93.3%)

DISCUSSION

The presently examined multi-drug regimen of Taxane & Platin in concurrent chemo radiation for locally advanced carcinoma cervix has previously been shown to yield superior outcomes relative to other cisplatin-based regimens. The use of concurrent chemo radiation has increased the 5-y OS rate of patients with locally advanced carcinoma cervix significantly, by up to 6%[5].

Traditionally, locally advanced carcinoma cervix has included FIGO stage IIb-IVa lesions. Though many oncologists now consider FIGO stages Ib2 and IIa2 to be locally advanced lesion. Paclitaxel (PTX), a taxane compound, has been shown to have high efficacy against solid tumours, especially epithelial ovarian cancer, lung, and breast cancer tumours. PTX cytotoxicity of human cervical cancer cells has been shown to involve inhibition the Raf-1 kinase activity. PTX inhibits mitosis by binding tubulin, a structural protein that is necessary for cell division, keeping tumour cells stuck in the G2 and M phases. PTX also appears to contribute to re-oxidation of hypoxic tumour cells[6]. Thus, it may function as radiation sensitizer, making it appropriate for use with RT.

In a phase II randomized trial comparing RT with concurrent weekly DDP(Cisplatin) or PTX in patients with LACC, Geara et al. did not find a significant advantage of PTX over DDP[7].

Moore et al. demonstrated that CCRT with TP was superior to CCRT with DDP alone in terms of ORR and progressive free survival in patients with LACC. Additionally, more recently, Umayahara et al. documented favourable anti-tumour activity of CCRT with Tp[8]

Due to additional cycle of neoadjuvant chemotherapy before CCRT, Miglieta et al. observed full complete clinical response rate and maintained local control. It was assumed that high dose of PTX (175 mg/m^2 every 3 weeks for four cycles) in chemotherapy regimen would contribute to favourable tumour regression in that study.

Varghese et al.[9] presented relatively lower response rate of 88%, even with dose-dense concurrent chemotherapy regimen of cisplatin 30 mg/m^2 and paclitaxel 40 mg/m^2 for 4 weeks along with radiotherapy.Though the authors considered no extra benefit with additional use of paclitaxel in the chemoradiation, we should notice that high rate of lost on follow-up might increase reporting biases in that study.

Similarly, Ke et al. launched concurrent chemotherapy with weekly application of DDP (20 mg/m^2) and taxotere (35 mg/m^2) for 4-5 weeks combining with daily radiation therapy (total dose of 65-80 Gy).

In our study, chemotherapy consisted of cisplatin (40 mg/m^2, weekly) and Paclitaxel (35 mg/m^2, weekly), every weeks, and radiotherapy with biological equivalent dose of 80 – 90 Gy to point A. High proportion of bulky tumour (14/30) and extensive invasion of local regional area (FIGO stage IIIA-IVA 18/30) might lead to mild early remission.

All patients finished full TP courses with a full RT course. The median RT time in our study was 61.5 days, similar to the 63-days median reported by Migliettaet al.[10]

Acute toxicities in our trial were generally tolerable and mild. Grade II bone marrow suppression in slightly more than a half of the cohort, Grade II, Grade III GI toxicity were seen in 30% and 23% of patients respectively. Most concerning was Grade IV skin toxicity in 4 (13.3%) patients. In a Trial done by Pabitra et al with same doses of paclitaxel and cisplatin, patients had Grade II & III GI toxicity (diarrhoea)[11].

No grade IV hematotoxicity was observed. Although vaginitis, proctitis, and cystitis were less common, they were mild (grade I) in few number of patients.

Ke et al.'s regime produced an 82.1% rate of myelosuppression (grade I, II, or III; no grade IV). A third of the patients in Miglietta et al.[12] study showed grade 3 or 4 hematological toxicity, whereas slightly more than three quarters of the patients in Sood et al.'s[13] study experienced grade III or IV acute hematological toxicity.

Comparing the toxicities of CCRT with DDP plus 5- fluorouracil versus CCRT with DDP plus PTX in patients with LACC, Sol et al.[5] found that the latter group had a higher frequency of severe (grade III or IV) leukopenia (79.2% vs. 11.1%) but a lower frequency of severe nausea (14.6% vs. 33.3%).

Study by Kalaghchi B et al was initiated to assess whether the combination of paclitaxel (35mg/m2) and cisplatin (30mg/m2) with radiation might feasible in primary untreated squamous cell carcinoma of the cervix with FIGO stages IB2 to IIIB. There was a complete response rate of 84% after 3 months. The major toxicity was grade 1 and 2 aneamia (92%). The regime was well tolerated in contrast to other studies[14].

CONCLUSION

We conclude that, a concurrent chemo radiation regime Cisplatin (40mg /m2) with Paclitaxel (35mg /m2) produced satisfactory short-term efficacy with relatively tolerable acute toxicities and feasibility among women attending our institute. This study was limited by a small sample size and short follow up. Further observation of the safety and efficacy of this regime is needed to ascertain its long-term effects.

Table 1: Distribution of Stage

Stage	
IIB	12 (40%)
IIIA	2 (6.7%)
IIIB	4 (13.3%)
IIIC	6 (20%)
IVA	6 (20%)

Table 2: Distribution of Skin toxicity, GI Toxicity (diarrhoea)

Skin toxicity	Grade 0	4 (13.3%)
	Grade 1	13 (43.3%)
	Grade 2	7 (23.3%)
	Grade 3	2 (6.7%)
	Grade 4	4 (13.3%)
GI Toxicity (diarrhoea)	Grade 0	0
	Grade 1	14 (46.7%)
	Grade 2	7 (23.3%)
	Grade 3	9 (30%)
	Grade 4	0

Table 3: Distribution of Haematological toxicity in Hb%, Haematological toxicity in TLC and Renal toxicity - (serum Creatinine)

Haematological toxicity in Hb%	Grade 0	0
	Grade 1	0
	Grade 2	25 (83.3%)
	Grade 3	5 (16.7%)
	Grade 4	0
Haematological toxicity in TLC	Grade 0	11 (36.7%)
	Grade 1	2 (6.7%)
	Grade 2	17 956.7%)
	Grade 3	0
	Grade 4	0
Renal toxicity - (serum Creatinine)	Grade 0	7 (23.3%)
	Grade 1	14 (46.7%)
	Grade 2	9 (30%)
	Grade 3	0
	Grade 4	0

Table 3: Distribution of Treatment time and Treatment response

Treatment time	Average	60.67 days
	Median	61.5 days
Treatment response	CR	28 (93.3%)
	PR	2 (6.7%)
	Stable	0
	Progressive	0

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