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Original Research

A Prospective Interventional Study to Compare Induction Chemotherapy Followed by Definitive Chemoradiation Versus Definitive Chemoradiation in Locally Advanced Carcinoma Cervix Patients

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Background: Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death in women worldwide. Every year in India, 1,23,907 women are diagnosed with cervical cancer and 77,348 die from the disease. In India majority of patients of carcinoma cervix presented in locally advanced stage. Chemoradiation followed by brachytherapy is the standard of care for management of locally advanced cervical cancer but failure to control systemic disease occurs in one third of patients. Neoadjuvant chemotherapy, however, has been tested in various studies in cervical cancer for many years without success. In this study, we compared induction chemotherapy with 3weekly paclitaxel and cisplatin followed by chemo-radiation versus definitive chemo radiation.

Materials and Methods: In this study 100 histopathologically proven squamous cell carcinoma cervix, locally advanced patients were included,the study group (n=50) received induction chemotherapy followed by definitive chemoradiation while the control group (n=50) received definitive chemoradiation.

Results: The median age was 51 years (Range 32 – 65 years). Majority of patients was FIGO stage IIB (23%), IIIB (61%). In study arm 42 patients (84%) had complete response, and 7 patients (14%) had partial response. In control group 40 patients (80%) had complete response and 8 patients (16%) had partial response. Overall response rate was 98% in study group and 96% in control group. (p value=0.991, statistically insignificant). Grade 2 and 3 haematological toxicities were higher in study group as compare to control group. Among gastrointestinal toxicities (nausea, vomiting and diarrhea) grade 1 toxicity in study group and grade 2 toxicity in control group was slightly higher. (statistically insignificant).

Conclusion: Induction chemotherapy with paclitaxel and cisplatin prior to standard chemoradiation provides similar results to chemoradiation alone with respect to response to treatment. Complete response rate was better achieved in study arm. In developing countries like India with limited resources and increasing cancer patient’s burden, induction chemotherapy followed by chemoradiation can be an alternative to standard care without compromising outcome and with manageable toxicities.

Introduction

Cervical cancer is the fourth most common cancer worldwide and the fourth leading cause of cancer death [1]. In the year 2020, approximately 604000 women were estimated to be diagnosed of having cervical cancer globally and 342000 women died due to this disease [2].

Carcinoma of uterine cervix is the most common gynaecological malignancy seen in Indian females with the peak age 45–54 years. Every year in India, 1,23,907 women are diagnosed with cervical cancer and 77,348 die from the disease. In India, higher incidence and mortality are due to lack of awareness of cervical cancer among population and most of women are reluctant to be screened regularly, present with locally advanced disease. Because of difference in disease spectrum of cancer cervix and associated problem for treatment and supportive measures, management of locally advanced disease poses a formidable challenge to the oncologist [3].

Standard treatment for most of patients with locally advanced disease is radiation therapy using a combination of external beam radiation with concurrent chemotherapy and brachytherapy. There are potential therapeutic advantages of giving chemotherapy prior to concurrent chemoradiotherapy. The rationale for the use of induction chemotherapy are multiple. Induction chemotherapy may increase radio sensitivity, decrease tumor size, prevent micro metastasis and significant reduction in systemic relapse [4, 5]. However, role of induction chemotherapy followed by radiation only or by concurrent chemoradiotherapy or by surgery is controversial because no significant survival advantages have been shown and may compromise patient’s immunity and ability to receive definitive treatment [6].

Due to escalating burden of malignancy and limited availability of radiotherapy facility, delay in initiation of definitive treatment is a common problem. In such cases giving induction chemotherapy is the only available immediate treatment modality. So this study was intended to find out the role of induction chemotherapy in locally advanced cervix cancer. The present prospective interventional study was conducted to compare induction chemotherapy (IC) followed by concurrent chemoradiation and definitive chemoradiation in locally advanced carcinoma cervix patients with respect to treatment outcomes in terms of toxicity profile and locoregional control.

Aim and Objectives

• To compare induction chemotherapy followed by concurrent chemoradiation and definitive chemoradiation in locally advanced carcinoma of cervix.

• To evaluate primary tumor response and loco-regional control.

• To evaluate treatment related acute toxicity.

Materials and Methods

This prospective randomized study was conducted in the tertiary cancer center, from June 2021 to May 2022. Total 100 women aged 18 to 70 years with newly diagnosed histopathologically confirmed squamous cell carcinoma of cervix having FIGO stage IIB–IIIC (FIGO staging 2018) were included in the study after taking permission from institutional ethical committee. Eastern Cooperative Oncology Group performance status was 0-2 with adequate baseline organ function (Hematological, RFT&LFT) of all patients. Informed consent was obtained from all patients before enrolment in this study. Patients with hypersensitivity to cisplatin or paclitaxel, previous history of radiotherapy and those with severe co-morbidity and having distant metastasis were excluded from the study.

The pre-treatment evaluation included detailed history, complete physical examination including gynecological examination, hematological and biochemistry studies, chest radiography, ultrasound

abdomen & pelvis and CECT abdomen & pelvis or MRI pelvis was done. All patients underwent biopsy to obtain histopathological proof of cancer. Staging was done according to the FIGO staging system.

Patients were randomized into two arms –

Arm A (Study Arm):-Fifty patients were treated with induction chemotherapy followed by concurrent chemoradiotherapy and brachytherapy

Arm B (Control Arm):-Fifty patients were treated with

definitive chemoradiotherapy and brachytherapy

Chemotherapy Technique

Study arm patients were treated with two cycles of induction chemotherapy with each cycle three weeks apart, consisting of the injection paclitaxel in a dose of 175 mg/m^2 intravenous infusion over 3 hours in normal saline 500 ml and injection cisplatin 75mg/m^2 intravenous infusion over 1-2 hours in 500ml normal saline with premedication and adequate hydration.

All patients treated with concurrent weekly cisplatin at dose of 30 mg/m^2 intravenous infusion in 500 ml normal saline with premedication and adequate hydration before radiotherapy.

Radiation Technique

All patients were treated with External Beam Radiotherapy (IMRT) by LINAC of total dose to whole pelvis 50Gy in 25 fractions over five weeks upfront in control group and upfront in control group and after 3 weeks of completion of 2^{nd} cycle of induction chemotherapy. Intracavitary Brachytherapy was delivered weekly after completion of 1week of EBRT with HDR technique with cobalt-60 source at the dose of 700cGy per fraction in 3 fractions. The plan of the treatment is to prescribe a total dose of 80-90 Gy at point A.

Statistical Analysis

Quantitative data was expressed in means with standard deviation and qualitative data was expressed in percentage proportions. Significance of difference in means of two group was inferred with unpaired T test. Significance of difference in means at various follow up period was inferred with repeated ANOVA test. Significance of difference in proportion in two groups was inferred with Chi-square test. For significance P value less than 0.05 has been considered as significant. The results of study group was analyzed & compared with control group in terms of various aspects like compliance, side effects, tumor response, & local disease status. All analysis were performed using IBM SPSS statistics, version 20 for windows.

Follow Up

Patients were examined for Tumor response and toxicity at the completion of treatment, at 3 and 6 months.

Tumor response evaluation was done based on RECIST

1.1 (Response Evaluation Criteria in Solid Tumors) criteria and toxicities were assessed as per Common Terminology Criteria for Adverse Events (CTCAEv5.0).

Results

A total of 50 patients in study arm and 50 patients in control arm were analysed.The clinical pathological characteristics were well balanced and there was no major difference in age distribution and ECOG performance status. Majority of patients in both arms were stage IIIB and mostly were well differentiated squamous cell carcinoma. At the end of induction chemotherapy in study arm majority of patients had only partial response (Table 1).

Patient Characteristics	Study Arm	Control Arm
Number of Patients	50	50
Mean Age (year)	51.68	50.44
ECOG Status (%)		
0	04 (8)	03 (6)
1	35 (70)	32 (64)
2	11 (22)	15 (30)
Histopathology (%)		
WDSCC	31 (62)	32 (64)
MDSCC	11 (22)	11 (22)
PDSCC	08 (16)	07 (14)
FIGO Stage (%)		
IIB	12 (24)	11 (22)
IIIA	05 (10)	07 (14)
IIIB	30 (60)	31 (62)
IIIC	03 (6)	01 (2)
Clinical Response of Induction chemotherapy (%)		
CR	0 (0)	-
PR	40 (80)	-
SD	10 (20)	-

Table 1. Baseline Patient Characteristics.

In study arm 16 (32%) patients developed grade 2 anaemia while in control arm 13 (26%) patients developed grade 2 anaemia. Grade 3 anaemia was presented in 7 (14%) patients in study arm only. Neutropenia grade =<2 was presented in 27 (52%) & 25 (50%) patients in study and control arm respectively. Six patients developed grade 3 neutropenia in study arm only. In study arm 12 (24%) patients developed grade 2 thrombocytopenia while in control arm 4 (8%) patients developed grade 2 thrombocytopenia. Eight patients developed grade 3 thrombocytopenia in study arm.

Among non-hematological toxicities nausea/vomiting grade =<2 was presented in 34 (68%) & 32 (64%) patients in study arm and control arm respectively. Grade 2 and grade 3 diarrhoea was slightly higher in control arm but statistically insignificant. In study arm 10 (20%) patients developed grade 1 toxicity and 3 (6%) patients developed grade 2 nephrotoxicity, while in control arm 15 (30%) patients developed grade 1 nephrotoxicity and no grade 2 nephrotoxicity seen. Grade=<2 skin toxicity was presented in 40 patients in study arm and 42 patients in control arm (Table 2).

	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control

Anaemia	11	14	16	23	16	13	7	0	0	0
Neutropenia	18	25	14	18	12	7	6	0	0	0
Thrombocytopenia	12	28	18	18	12	4	8	0	0	0
Nausea	11	15	24	20	10	12	5	3	0	0
Vomiting	9	17	25	20	10	9	6	4	0	0
Diarrhoea	28	21	9	10	11	15	2	4	0	0
Nephrotoxicity	37	35	10	15	3	0	0	0	0	0
Skin toxicity	10	8	25	27	15	15	0	0	0	0

Table 2. Cumulative Toxicity Profile During Treatment.

At at one month of completion of treatment, 40 patients (80%) in study arm and 38 patients (76%) in control arm had complete response (CR). Partial response (PR) was presented in 8 patients (16%) &10 patients (20%) in both arm respectively. Two patients (4%) in the study arm as well as control arm had stable disease. After 3 & 6 months post treatment CR increased to 84% & 80% in study and control arm respectively. In study arm one out of two patients of stable disease converted in partial response while one out of two patients of stable disease converted to progressive disease in control arm (Table 3).

Complete response			Partial response		Stable disease		Progressive disease	
	Study	Control	Study	Control	Study	Control	Study	Control
1 month	40	38	8	10	2	2	0	0
3 months	42	40	7	8	1	1	0	1
6 months	42	40	7	8	1	1	0	1
P value	0.101 (NS)		0.148 (NS)		1.000 (NS)		0.116 (NS)	

Table 3. Treatment Response.

Discussion

The standard treatment for locally advanced cervical cancer (LACC) is concurrent chemo-radiation (CCRT). The overall survival (OS) for stage IIB is approximately 60–65% and for stage III–IV cancer only a dismal 25–50%. Hence, there is a constant quest to develop new strategies in treatment to improve survival. Chemotherapy prior to radiotherapy is known to reduce the volume of the disease, making subsequent irradiation or surgery more effective and also reducing the micro metastatic disease. The incidence of advanced cervical cancer is high especially in developing countries. The most important factor contributing to this is the limited access to radiotherapy facilities resulting in a delay in treatment initiation [7]. This problem of scarcity can be overcome if the benefit of IC is demonstrated and yield improved The results from two studies [8, 9] reported on patients who received IC using weekly paclitaxel (60–80 mg/m2) and carboplatin (AUC = 2) for 6 weeks followed by CCRT showed that following IC, a response rate of 67.8–72.7% was achieved. However, these responses were mostly partial. Post- CCRT, the response rate increased to approximately 90%. A 3-year overall survival rate of 67% was observed in stage IB2-IVA patients. Thus, the literature has shown equivocal results with respect to the utility of IC preceding radiotherapy. The present study was carried to assess the efficacy and safety profile of induction chemotherapy followed by concurrent chemoradiation and compare it with standard definitive concurrent chemoradiation in locally advanced carcinoma cervix. At the end of treatment, clinically complete response was 80% in study arm and 76% in control arm while partial response was presented in 16% & 20% patients in respective arms. At 3 and 6 months follow up after treatment, in study arm, complete response was 84% versus 80% in control arm. Overall response rate was

98% and 96% in study arm and control arm respectively at 6 months of follow up. Similar results were found in the study conducted by Fotedar et al [10]. In this study, 38 (73.08%) patients achieved CR and 13 (25%) had residual disease in study group while in control group 41 (75.93%) patients achieved CR and 12 (22.22%) had outcomes.

residual disease. Patients were followed up for a period of 3 years with cumulative survival of 64.15% and 66.66% in study and control arm respectively. Though the p value was insignificant the study supported the usage of IC followed by CT/RT and concluded that similar results are seen with CT/RT alone.

Narayan et al. [11] retrospectively compared the effect of 2 cycles of thrice weekly TPF (cisplatin + paclitaxel + 5-fluorouracil) or TF (cisplatin + 5-fluorouracil) followed by CCRT vs. CCRT alone in 723 stages IIB–IIIB cervical cancer patients. They found that IC followed by CCRT could improve 5-year progression-free survival (58.3% vs. 41.8%) but had no impact on the overall survival.

Marita et al. [12] retrospectively analysed the survival of 207 stage IIB–IIIB cervical cancer patients who received 2–4 cycles of platinum-based IC prior to CCRT. The results revealed that the 5-year survival rates for stage IIB–IIIA and IIIB were 84% and 61%, respectively, which are superior to the survival rates of traditional CCRT reported in the literature.

The results of the phase III trial of induction chemotherapy with weekly cisplatin and paclitaxel followed by chemoradiation for locally advanced cervical cancer conducted by Jing Li et al [13] demonstrated that after a median follow-up of 28 months, the 3-year OS rate was 83.9%, and the 3-year PFS rate was 73.6%. The study concluded that four cycles of IC with cisplatin (40 mg/m^2) and paclitaxel (60 mg/m^2) weekly followed by CCRT is feasible and showed a preferable response rate. IC-responsive patients had superior PFS and OS compared with IC-nonresponsive patients.

McCormack M et al [14] investigated the feasibility of weekly dose dense NACT with paclitaxel (80mg/m^2) and carboplatin (AUC2) before chemoradiation. A good response rate was achieved. OS and 3 year PFS were 67% and 68% respectively.

Roberto Angioli et al [15] evaluate the efficacy and safety of NACT with carboplatin (AUC6) and paclitaxel (175mg/m^2) in locally advanced stage IB2-IIB cervical cancer. The overall clinical response rate was 78.3% including 43.5% with complete response and 34.8% with partial response after NACT. Most common toxicity was grade 1and 2 hematological and nausea/vomiting.

In this study there was no statistically significant toxicity between the study and control group. Haematological toxicities (anaemia, neutropenia, thrombocytopenia) were slightly higher in study group but not statistically significant whereas diarrhoea and nephrotoxicity were slightly higher but not statistically significant in control group. Nausea and vomiting were slightly higher in study group but not statistically significant. The results of toxicity seen in our study were also similar to the study conducted by Duenas- Gonzalez et al. [16].

In conclusion, we conclude that, in developing countries like India with limited resources and increasing cancer patient’s burden, and impact of delay in the initiation of radiation therapy in the course of disease, induction chemotherapy followed by chemoradiation can be an alternative to standard care in locally advanced carcinoma cervix patients without compromising outcome with manageable toxicities.

Larger sample size, longer duration of follow up may be needed to establish it as standard of care.

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Statement of Transparency and Principals:

• Author declares no conflict of interest

• Study was approved by Research Ethic Committee of author affiliated Institute.

• Study's data is available upon a reasonable request. All authors have contributed to implementation of this research.

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