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Original Article

Comparative Evaluation of Radiotherapy with Concurrent Weekly Cisplatin versus Concurrent Daily Erlotinib and Weekly Cisplatin in Locally Advanced Carcinoma Cervix

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Abstract

Background: Erlotinib is an oral epidermal growth factor receptor tyrosine kinase inhibitor. Early phase clinical trials of Erlotinib in combination with cisplatin-based concurrent chemoradiotherapy (CCRT) in locally advanced carcinoma cervix have demonstrated improved antitumor responses with mild toxicity profile; however, the evidence available on this is limited. We prospectively evaluated the efficacy and safety of Erlotinib (150 mg/day) with CCRT in locally advanced carcinoma cervix and compared with standard CRT.

Materials and Methods: In this prospective, comparative study, 60 locally advanced carcinoma cervix patients received either Erlotinib (150 mg/day) with CRT or CRT. Treatment CRT included cisplatin 40 mg/m2 intravenously weekly concurrently with external beam radiation followed by intracavitary brachytherapy. Tumor response was calculated as per the WHO criteria. Toxicity and adverse events (AEs) were assessed as per CTCAE v 3.

Results: The higher number of patients achieved a complete response in the Erlotinib plus CRT group than the CRT group (28/30, 93.3% vs. 21/30, 70%, $P < 0.05$), which was statistically significant. The AEs commonly encountered in both the treatment groups were majority of Grade 1/2. A higher incidence of diarrhea and skin reaction was noted in the Erlotinib plus CRT group in comparison CRT, whereas the incidence of nausea and vomiting was higher in the CRT group. No Grades 4 and 5 toxicity was observed in Erlotinib with CRT. Erlotinib was observed to be safe with manageable toxicity profile.

Conclusion: Erlotinib 150 mg daily can be safely added to cisplatin-based CCRT in locally advanced carcinoma cervix, to achieve better therapeutic response without potentiating the toxicity.

Key words: Advanced, Carcinoma, Cervix, Epidermal growth factor receptor, Erlotinib, Neoplasms, Squamous cell, Tyrosine kinase inhibitor

INTRODUCTION

Globally, cervical cancer is the fourth most common cancer in women, with an estimated 560,505 new cases and 284,923 deaths in 2015.[1] Cervical cancer is a preventable disease and a major cause of morbidity and mortality, particularly in developing countries.[2] In India, cervical cancer is the second most common cancer, with an estimated 132,314 new cases and 73,337 deaths in the year 2015.[1,3]

In India, population-based cervical cancer screening is largely nonexistent in most regions due to competing healthcare priorities, insufficient financial resources and a limited number of trained providers.[3] With 60–80% of the cases presenting in locally advanced stage,[4-6] management of the carcinoma cervix remains challenging in Indian scenario.

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Several studies have shown the superiority of platinum-based therapy, combined with radiation when compared to radiotherapy alone. Based on these premises the concomitant administration of radiotherapy plus weekly cisplatin is considered standard of care[7] However, despite the benefits obtained with the addition of platinum-based chemotherapy the cure rates of locally advanced squamous cell carcinoma have reached a plateau in recent years.[2,8,9]]

Epidermal growth factor receptor (EGFR) is a 170-kDa transmembrane glycoprotein receptor dimerizes to activate a tyrosine kinase (TK) domain that modulates multiple functions, including cell differentiation, growth, gene expression, and development. The EGFR is frequently overexpressed in cervical dysplasia and cervical cancer, and patients who have high levels of EGFR in their tumors have a poor prognosis.[10] A recent meta-analysis confirmed that EGFR overexpression is closely associated with reduced survival in patients with cervical cancer. Therefore, EGFR represents a valid target for preventing tumor growth and metastasis, and anti-EGFR therapies are been explored to improve outcomes in cervical cancer.[11]

Erlotinib is an oral and well-tolerated drug that reversibly binds to the intracellular catalytic domain of EGFR TK, thereby reversibly blocking EGFR phosphorylation, the signal transduction events and tumorigenic effects associated with EGFR activation.[12] Phase I and II trials of Erlotinib in combination with cisplatin-based concurrent chemoradiotherapy (CCRT) in locally advanced carcinoma cervix have demonstrated improved antitumor responses with manageable mild toxicity profile (diarrhea and rash).[12,13]

In the Phase II trial, majority (94.4%) patients on Erlotinib 150 mg/day in combination with CCRT achieved a complete response (CR). The 2-year and 3-year cumulative overall and progression-free survival rates were 91.7% and 80.6% and 80% and 73.8%, respectively.[13] These findings provided the foundation for the current study. Therefore, the present comparative study was carried out to evaluate the efficacy and safety of Erlotinib (150 mg/day) with CCRT in patients with locally advanced carcinoma cervix and compared with the CCRT alone.

MATERIALS AND METHODS

This was an open-labeled, prospective, comparative study carried out in patients with carcinoma of the cervix, attending Government Cancer Hospital, Netaji Subhash Chandra Bose Medical College Jabalpur (India), during the period of the year 2014–2015. The study was approved by the Institutional Ethical Committee and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

The study included patients with the following eligibility criteria: (1) Histopathologically proven squamous cell carcinoma of cervix, (2) International Federation of Gynecology and Obstetrics Stage IB2-IVA, (3) age 18–80 years, and (4) Eastern cooperative oncology group (ECOG) performance status of 0, 1, or 2.

We excluded the following patients: (1) Age ≤18 years, (2) inadequate hematologic, cardiac, renal, and hepatic functions, (3) history of allergy with similar biological to Erlotinib/Cisplatin, 4) evidence of distant metastases (Stage IVB), (5) prior radiotherapy/chemotherapy/surgery, (6) other synchronous malignancies, (7) uncontrolled infection/any other systemic diseases, (8) not willing for informed consent, and (9) pregnant and lactating females.

Before enrollment, all patients gave a full history and underwent a physical examination, complete blood count with differential, electrolyte assessment, liver and renal function tests, chest X-ray, electrocardiogram, ultrasonography abdomen and pelvis, abdominal and pelvic computed tomography (CT)/magnetic resonance imaging (MRI) and cystoscopy.

Two treatment groups (test group and control group) were defined. Patients were randomly allocated to either group to receive the treatment. Test group received Erlotinib plus CCRT treatment, while the control group received CCRT only.

In the control arm, patients received cisplatin 40 mg/m^2 intravenously weekly concurrently with external beam radiation (EBRT). Patients in the study arm received daily Erlotinib 150 mg plus cisplatin 40 mg/m^2 intravenously weekly concurrently with EBRT.

Radiotherapy Treatment Protocol Schedule (Both Arms)

EBRT was administered to the whole pelvic region using Co60 teletherapy machine (Theratron 780E) followed by the high dose rate (HDR)-intracavitary brachytherapy (ICBT). Cases were treated by conventional radiotherapy schedule as follows: (1) EBRT = 5000 cGy, (2) HDR-ICBT = 700 cGy X 3 # Point A and 3) Total Dose = 8000 cGy in Point A.

EBRT was given for 5 days a week with a total duration of 35 days, and after completion of EBRT, 3 fractions of weekly HDR-ICBT were given. Total duration of completion of the treatment with EBRT and ICRT was 56 days. Portals for EBRT of pelvis: Parallel opposed (anterior-posterior fields)/four field box techniques.

Concurrent Chemotherapy Protocol Schedule

Control group: Cisplatin 40 mg/m2 4 weekly (ceiling dose 70 mg)

In the control group, patients received weekly cisplatin 40 mg/m^2 IV in 300 ml normal saline over 1 h. Premedication with dexamethasone 8 mg, omeprazole 20 mg, and 5-HT3 antagonist as antiemetic was given, with adequate hydration for 2 h before and after the chemotherapy.

Test group: Daily Erlotinib 150 mg OD plus Cisplatin 40mg/m2 4 weekly (ceiling dose 70 mg)

In the test group, patients received daily tablet Erlotinib 150 mg OD before food and were started 1 week before radiation to achieve a stable blood level and were continued until the past day of irradiation. Along with this, weekly Cisplatin 40 mg/m^2 IV in 300 ml normal saline was started from day 1 of radiation.

Patients (in both control and test group) receiving CRT were assessed weekly for symptomatic, clinical improvement, and adverse reactions patients were evaluated at the end of treatment completion and 1st, 3rd, and 6th months follow-up visits.

Parameters evaluated

The tumor response in both the groups was evaluated using the WHO criteria/response evaluation criteria in solid tumors (RECIST version 1.1) criteria. The response outcomes assessed included CR, partial response (PR), progression of disease, and stable disease based on CT/MRI findings. Adverse events (AEs) were assessed and graded by common toxicity criteria for AEs (version 3.0) and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer acute radiation criteria.

Statistical Analysis

Statistical analysis was performed with software (SPSS, version 19). Descriptive statistics were used to express the data. For categorical variables, Chi-square or Fischer exact test were used as appropriate. $P \leq 0.05$ was considered to indicate a statistically significant difference.

RESULTS

The patients were collected from 2014 to 2015, and a total of 60 patients of locally advanced carcinoma cervix were enrolled in this comparative study. 30 patients were enrolled in test arm, and 30 were enrolled in the control arm. The mean age of the patients in the test arm was 45.6 ± 6.3 years, and in the control arm, it was 54.7 ± 10.4 years. In both the groups, majority patients were from lower socioeconomic status and had ECOG status of 1. The baseline characteristics of locally advanced carcinoma cervix patients enrolled in the two treatment groups are summarized in Table 1.

Tumor Response

We observed that higher number of patients achieved CR in the Erlotinib with CRT group than in the CRT alone group (28/30, 93.3% vs. 21/30, 70%). Statistically (Chi-square value = 5.45, P < 0.05) the treatment response observed in the Erlotinib with CRT was significant higher [Table 2].

Safety and Toxicity

All AEs commonly encountered in both the treatment groups were of Grades 1/2/3. A higher incidence of skin reaction [Table 3] and diarrhea [Table 4] was noted in the Erlotinib with CRT group in comparison to CRT alone, whereas the incidence of nausea and vomiting was higher in the CRT group [Tables 5 and 6]. Only <10% of cases in either of the groups developed urinary tract infections. No Grades 4 and 5 toxicity was observed in Erlotinib with CRT group. Erlotinib was observed to be safe with manageable toxicity profile.

Table 1: Baseline characteristics of locally advanced carcinoma cervix patients in the treatment groups

Characteristics	Erlotinib plus concurrent CRT (study group=30)	Concurrent CRT (control group=30)
Age in years (%) Mean±SD	45.6±6.3	54.7±10.4
Age group in years (%)		
30–39	3 (10)	2 (6.7)
40–49	16 (53.3)	6 (20)
50–59	10 (33.3)	8 (26.7)
60–69	1 (3.3)	11 (36.7)
>70	0 (0)	3 (10)
Performance status (%)		
ECOG 1	28 (93.3)	26 (86.7)
ECOG 2	2 (6.7)	4 (13.3)
Tobacco chewer (%)		
Yes	27 (90)	28 (93.3)
No	3 (10)	2 (6.7)
Socioeconomic status		
Lower	28 (93.3)	29 (96.7)
Middle	2 (6.7)	1 (3.3)
FIGO disease stage (%)		
IIA	5 (16.7)	5 (16.7)
IIB	13 (43.3)	9 (30)
IIIA	4 (13.3)	9 (30)
IIIB	6 (20)	3 (10)
IV-A	2 (6.7)	4 (13.3)
Chemotherapy cycles total completed		
3 cycles	0 (0)	4 (13.3)
4 cycles	2 (6.7)	9 (30)
5 cycles	28 (93.3)	17 (56.7)

FIGO: International Federation of Gynecology and Obstetrics, SD: Standard deviation, ECOG: Eastern Cooperative Oncology Group

Table 2: Response to treatment in the test group and control group

Response to treatment	*n* (%)		Chi-square value	*P*
	Erlotinib plus CCRT	CCRT		
CR	28 (93.3)	21 (70)	5.45	<0.05
PR	2 (6.7)	9 (30)		
Total	30	30		

CR: Complete response, PR: Partial response, CCRT: Concurrent chemoradiotherapy

Table 3: Incidence of skin reaction in the test group and control group during treatment period

AEs-skin reaction	*n* (%)			
	Erlotinib plus CCRT (study group=30)		CCRT (control group=30)	
Skin reaction (treatment week)	Grade 1	Grade 2	Grade 1	Grade 2
1st	0	0	0	0
2nd	0	0	0	0
3rd	4 (13.3)	0	2 (6.7)	0
4th	16 (53.3)	3 (10.0)	2 (6.7)	1 (3.3)
5th	20 (66.7)	6 (20.0)	5 (16.7)	1 (3.3)
6th	25 (83.3)	4 (13.3)	5 (16.7)	0
7th	27 (6.7)	3 (93.3)	5 (16.7)	0

CCRT: Concurrent chemoradiotherapy, AEs: Adverse events

Table 4: Incidence of diarrhea in the test group and control group during treatment period

AEs-diarrhea	*n* (%)					
	Erlotinib plus CCRT (study group=30)			CCRT (control group=30)		
Diarrhea (treatment week)	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
1st	13 (43.3)	14 (46.7)	0	1 (3.3)	0	0
2nd	15 (50)	8 (26.7)	6 (20)	3 (10)	0	0
3rd	5 (16.7)	4 (13.3)	8 (26.7)	3 (10)	1 (3.3)	0
4th	5 (16.7)	1 (3.3)	0	3 (10)	3 (10)	0
5th	1 (3.3)	0	0	5 (16.7)	2 (6.7)	0
6th	1 (3.3)	0	0	2 (6.7)	0	0
7th	0	1 (3.3)	0	1 (3.3)	0	0

CCRT: Concurrent chemoradiotherapy, AEs: Adverse events

DISCUSSION

The findings of the present comparative study indicate that addition of Erlotinib to CCRT results in improved tumor response compared to CCRT in patients with locally advanced carcinoma cervix.

The treatment of carcinoma cervix has witnessed major changes over the past few decades, from radium therapy alone to combination of external beam radiotherapy (EBRT) and ICBT, and finally to CCRT.[9] Backed up with the results of randomized control trials, which showed an improvement in survival with the use of CCRT, the National Cancer Institute issued a clinical alert to establish CCRT as the standard treatment for carcinoma cervix.[9,14]

Cisplatin-based CRT is the standard treatment for cervical cancer.[7,14] However, despite the benefits obtained with the addition of platinum-based chemotherapy the cure rates of locally advanced squamous cell carcinoma have reached a plateau in recent years.[2,8,9] In the further quest for improving the outcomes, biological agents are being explored.

EGFR is frequently overexpressed in human papillomavirus (HPV)-associated dysplasias and carcinomas, suggesting that it might play a role in the activation of signaling pathways.[15] A meta-analysis demonstrated that EGFR overexpression is closely associated with reduced survival in patients with cervical cancer. These results facilitate the individualized management of clinical decisions for anti-EGFR therapies in cervical cancer patients.[11]

Erlotinib is an oral EGFR TK inhibitor that reversibly competes with ATP for binding the TK domain of EGFR, thereby reversibly blocking EGFR phosphorylation, the signal transduction events and tumorigenic effects associated with EGFR activation.[12] Erlotinib has been found to prevent immortalization of cultured human cervical epithelial cells by the complete HPV-16 genome

Table 5: Incidence of nausea in the test group and control group during treatment period

AEs-nausea	*n* (%)					
	Erlotinib plus CCRT (study group=30)			CCRT (control group=30)		
Nausea (treatment week)	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
1st	0	0	0	0	0	0
2nd	4 (13.3)	0	0	2 (6.7)	0	0
3rd	3 (10)	2 (6.7)	1 (3.3)	6 (20)	3 (10)	5 (16.7)
4th	3 (10)	2 (6.7)	0	5 (16.7)	4 (13.3)	5 (16.7)
5th	3 (10)	1 (3.3)	0	5 (16.7)	3 (10)	2 (6.7)
6th	5 (16.7)	0	0	5 (16.7)	4 (13.3)	1 (3.3)
7th	2 (6.7)	0	0	7 (23.3)	3 (10)	0

CCRT: Concurrent chemoradiotherapy, AEs: Adverse events

Table 6: Incidence of Vomiting in the test group and control group during treatment period

AEs-vomiting	*n* (%)			CCRT (control group=30)		
	Erlotinib plus CCRT (study group=30)					
Nausea (treatment week)	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
1st	0	0	0	2 (10)	2 (6.7)	0
2nd	4 (13.3)	0	0	4 (13.3)	2 (6.7)	2 (6.7)
3rd	3 (10)	2 (6.7)	1 (3.3)	6 (20)	3 (10)	5 (16.7)
4th	3 (10)	2 (6.7)	0	4 (13.3)	3 (10)	5 (16.7)
5th	3 (10)	1 (3.3)	0	5 (16.7)	3 (10)	2 (6.7)
6th	5 (16.7)	0	0	5 (16.7)	4 (13.3)	1 (3.3)
7th	2 (6.7)	0	0	7 (23.3)	3 (10)	0

CCRT: Concurrent chemoradiotherapy, AEs: Adverse events

or the E6/E7 oncogenes. Erlotinib stimulates apoptosis in cells that express HPV-16 E6/E7 proteins and induces senescence in a subpopulation of cells that did not undergo apoptosis.[16]

Clinical trials have demonstrated encouraging antitumor activity alone or in combination with chemotherapy and exhibited radiosensitizing effects in a variety of malignancies.[17-20] Early phase clinical trials of Erlotinib in combination with cisplatin-based CCRT in locally advanced carcinoma cervix have demonstrated improved antitumor responses with manageable mild toxicity profile (diarrhea and rash, with no hematological side effects).[12,13] Based on the promising antitumor outcomes document in early phase, clinical trials,[12,13] the present study evaluated the safety and efficacy of cisplatin-based CCRT with or without daily Erlotinib in locally advanced carcinoma cervix in India.

In the present comparative study, we found that addition of Erlotinib to the CCRT resulted in improved tumor response rate than CCRT alone in locally advanced squamous cell cervical cancer. The higher number of patients achieved CR in the Erlotinib with CRT group than in the CRT alone group (28/30, 93.3% vs. 21/30, 70%, $P < 0.05$), which was statistically significant. The findings of improved tumor response with the addition of Erlotinib to CRT are similar to the findings of two clinical trials.[12,13]

In the Phase 1 trial, Nogueria-Rodrigues *et al*.[12] evaluated the maximum tolerated dose and the safety of Erlotinib in combination with cisplatin-based CRT in locally advanced (Stage IB-IVA squamous cell carcinoma) cervical cancer. Patients received escalating doses of Erlotinib (50/100/150 mg) combined with cisplatin (40 mg/m^2, weekly, and 5 cycles) and radiotherapy (external beam 4500 cGy in 25 fractions, followed by 4 fractions/600 cGy/weekly of brachytherapy). Out of 12 evaluable patients, 11 (91.7%) experienced a CR and 1 (8.3%) PR at the end of combined treatment. Two of 12 patients have had disease progression after 12 months of follow-up. The most common AEs noted were skin rash followed by diarrhea, which were manageable. Most of the AEs were either Grade 1 or 2, with few of Grade 3. No Grade 4 toxicities or treatment break/treatment-related deaths due to toxicity occurred in the trial. The authors found that the maximum tolerated a dose of Erlotinib that could be given along with cisplatin-based CCRT was 150 mg. The addition of Erlotinib to cisplatin-based CCRT was found to be safe and well tolerated.[12] Since the results were highly encouraging it gave the investigators a boost to proceed to Phase II trial.

In the Phase II trial, Nogueira-Rodrigues *et al*.[13] evaluated Erlotinib dose of 150 mg/day in combination with cisplatin-based CRT in locally advanced (Stage IIB-IIIB) cervical cancer. Patients received Erlotinib at a dose of

150 mg/day 1 week before and in combination with cisplatin (40 mg/m^2 administered weekly for 5 cycles) and radiotherapy (4500 centigrays in 25 fractions), followed by brachytherapy (4 fractions at a dose of 600 centigrays weekly). A total of 36 patients completed treatment with Erlotinib and CRT. The median duration of therapy was 77 days and the median follow-up period was 59.3 months. The therapy was well tolerated overall, and 34 patients (94.4%) achieved a CR. The 2 and 3-year cumulative overall and progression-free survival rates were 91.7% and 80.6% and 80% and 73.8%, respectively. The most common AEs were skin rash, diarrhea, and nausea, which were Grade 1 or 2 in the majority of patients. The treatment did not lead to limiting in field toxicity, and there was no therapy related deaths reported. The combination of Erlotinib dose of 150 mg/day in combination with cisplatin-based CRT was found to be safe and exerts significant antitumor activity in locally advanced squamous cell cervical cancer.[13]

Perez Rodrigo *et al*.,[21] in a case report evaluated the effectiveness and safety of the use of Erlotinib in two cases of refractory cervical cancer. They observed that the progression-free survival was 6 months and 4 months in each case with minor adverse effects. They concluded that Erlotinib 150 mg/day presented similar results to those obtained from cisplatin doublets in women with refractory cervical cancer, with minor adverse effects, however, needed validation in larger populations.[21]

In the present comparative study, the AEs commonly encountered in both the treatment groups were majority of Grades 1/2. A higher incidence of diarrhea and skin reaction was noted in the Erlotinib with CRT group in comparison to CRT alone, whereas the incidence of nausea and vomiting was higher in the CRT group. In the Erlotinib group, most patients developed skin reaction during the 3rd or 4th week of treatment. The reactions that occurred in the field of irradiation were mostly desquamous type and were associated with severe itching. It was managed by oral antihistamines, topical emollients, and gentian violet. The desquamation subsided by the end of irradiation and new epidermal layer had formed by the 2nd month of full treatment completion. The skin reactions that developed outside the realm of irradiation were mostly of pimples type, and it developed mainly over the face and nasolabial fold; oral antihistamines and topical emollients were used in their treatment.

Similarly, majority presenting with Grade 1 diarrhea in the 1st and 2nd week of treatment in Erlotinib group and was managed by adequate hydration, antimotility drug, and probiotics. Only <10% of cases in either of the treatment groups presented with complaints of burning micturition fever and their routine urine examination revealed urine sample loaded with pus cells. The patients were diagnosed to have urinary tract infection, and they responded to broad spectrum I/V antibiotics Ciprofloxacin and metronidazole for 5 days. The incidence of urinary tract infections might be due to the unhygienic conditions that the patients live in and may not be due to chemotherapy or irradiation.

In the present study, no Grades 4 and 5 toxicity was observed in Erlotinib with CRT group. The AEs documented in the present study were similar to those events commonly documented in clinical trials.[12,13] Erlotinib was observed to be safe with manageable toxicity profile.

In summary, the addition of Erlotinib (150 mg/day) to standard cisplatin-based CCRT showed improved tumor response in comparison to cisplatin-based CCRT alone in locally advanced carcinoma cervix patients without producing additional toxicity. Although robust multicenter, randomized control trials with larger sample size are needed to validate these interesting results.

The study had limitations; the sample size was small, conducted in a single hospital setting and short-term treatment outcomes were assessed. Data on the long-term safety and survival benefits needs to be explored further.

CONCLUSION

Erlotinib (150 mg daily) can be safely added to cisplatin-based CCRT in locally advanced carcinoma cervix, to achieve better therapeutic response without potentiating the toxicity.

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