

**Original Research**

A Comparative Evaluation of Concomitant Chemoradiation with Weekly Cisplatin and Erlotinib versus Concomitant Chemoradiation with Weekly Cisplatin in Management of Locally Advanced Carcinoma Cervix

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Abstract

Purpose: The purpose was to compare feasibility, tolerability, toxicity and local control of concomitant chemoradiation with weekly cisplatin and erlotinib versus concomitant chemoradiation with weekly cisplatin in EGFR positive locally advanced carcinoma cervix.

Material and Methods: In this prospective, comparative study, 60 histopathologically proven locally advanced carcinoma cervix patients with EGFR positivity received either Erlotinib (150 mg/day) with concomitant chemoradiation (study group) or CCRT (control group). Treatment with CCRT included cisplatin 40 mg/m² intravenously weekly concurrently with external beam radiation (50 Gy in 25 fractions over 5 weeks) followed by intracavitary HDR brachytherapy (7Gy to point A three times, once in a week). Tumor response was calculated as per the WHO criteria. The treatment induced toxicity such as anaemia, leucopenia and nausea/vomiting were graded as per WHO criteria. Skin reaction, diarrhea and genitourinary toxicity were graded as per RTOG criteria.

Results: Overall, complete response was seen in 93% in study group and 86% in control group at the end of treatment. In stage IIB and IIIA, complete response was observed in 100% of patients in the study and control group. Sixty percent patients with stage IIIB in study group and control group had complete response. Forty percent patients with stage IIIB in two groups showed partial response. At last follow up, 93% patients in study group and 80% patients in control group were observed to be free of disease. There were 7% and 10% patients with residual disease in study group and control group respectively. Distant recurrence was seen in 10% patients in control group. Even though response was better in study group but the difference in two groups was not statistically significant.

The toxicities commonly encountered in both the treatment groups were majority of Grade I/II. A higher incidence of nausea, vomiting, diarrhea and skin rash was noted in the Erlotinib plus CCRT group in comparison CRT. No Grades 4 and 5 toxicity was observed in Erlotinib with CCRT. Erlotinib was observed to be safe with manageable toxicity profile.

Conclusion: Addition of Erlotinib to standard cisplatin-based CCRT showed improved tumor response in comparison to cisplatin-based CRT alone in treatment of locally advanced carcinoma cervix, although not statistically significant with manageable toxicity.

Keywords: Advanced, Carcinoma, Cervix, Epidermal growth factor receptor, Erlotinib, Tyrosine kinase inhibitor.

Introduction

Incidence and mortality of carcinoma cervix have declined in developed world over past few decades but it still remains to be the most common gynecological cancer. Globally it is the fourth most common malignancy in women. Every year around 569,847 new cases of carcinoma cervix are diagnosed worldwide and 311,365 die of the disease in a year.¹

Carcinoma cervix is the second most common cancer in women in India after breast cancer.¹ Every year approximately one lakh new cases are registered.² In developing countries more than 80% of women with carcinoma cervix are diagnosed at advanced stage.³ Screening for carcinoma cervix has led to a reduction in carcinoma cervix mortality by 40% since the onset of widespread screening.⁴

Concomitant chemoradiation with weekly cisplatin is considered to be the standard of care for locally advanced carcinoma cervix. A meta-analysis reported that chemoradiotherapy leads to 6% improvement in 5-year survival when compared with radiotherapy alone.⁵ However despite the use of concomitant chemoradiation with cisplatin in locally advanced carcinoma cervix, many patients have experienced locoregional failure (20-25%) and distant failure (10-20%).⁶ Epidermal Growth Factor Receptor (EGFR) is expressed in non-malignant cells, high or abnormal EGFR expressions were found in solid tumors like brain glioma, esophageal cancer, gastric cancer, breast cancer, lung cancer, ovarian cancer and carcinoma cervix.^{7,8} The expression of EGFR in various tumors has been correlated with disease progression, poor survival, poor response to therapy⁹, and the development of resistance to cytotoxic agents.^{10,11}

Erlotinib is an oral and well-tolerated drug which acts by competing reversibly with adenosine triphosphate (ATP) for binding to the tyrosine kinase domain of EGFR. It inhibits clonal growth, stimulates apoptosis, and induced premature senescence in HPV E6/E7 expressing cervical cells.¹²

In a phase I trial by Rodrigues et al, the maximum tolerated dose of Erlotinib was found to be 150 mg with skin rash being most common side effect.¹³ In the Phase II trial, 94.4% patients on Erlotinib 150 mg/day in combination with CCRT achieved a complete response. 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.¹⁴ In a study by Rawat et al, 93.3% and 70% patients achieved complete response in study group (erlotinib with CCRT) and CCRT group respectively.¹⁵

Material and Methods

This was an open-labeled, prospective, comparative study and included the patients with following eligibility criteria: (1) Locally advanced carcinoma of uterine cervix, (2) Epidermal growth factor receptor positivity, (3) FIGO stage IIB-III B, (4) Karnofsky Performance Status > 70, (5) Age 19-64 years.

Following patients were excluded: (1) EGFR negativity, (2) Age <19 years or >64 years, (3) inadequate hematologic, renal, and hepatic functions, (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.

Detailed history was taken from all the patients before enrollment. All the patients underwent general physical examination, and complete systemic examination including gynaecological examination (per-speculum, per-vaginal and per-rectal examination), complete blood count with differential, liver and renal function tests, chest X-ray, ultrasonography abdomen and pelvis. Abdominal and pelvic computed tomography (CT)/magnetic resonance imaging (MRI) and cystoscopy were done when needed.

The patients were divided randomly in two groups containing 30 patients in each group, using internet service website <https://www.random.org/lists/>.

Patients in the study arm received Tab. Erlotinib 150 mg PO OD concomitant with Inj. Cisplatin 40 mg/m² intravenously weekly concurrently with EBRT. In the control arm, patients received Inj. Cisplatin 40 mg/m² intravenously weekly concurrently with external beam radiation (EBRT).

Radiotherapy Treatment Protocol Schedule (Both Arms)

EBRT was administered to the whole pelvic region followed by the high dose rate (HDR)-intracavitary brachytherapy (ICBT). Cases were treated by conventional radiotherapy schedule as follows: (1) EBRT = 5000 cGy, given 5 days a week with total duration of 35 days by parallel opposed (anterior-posterior fields)/four field box techniques, (2) HDR-ICBT = 700 cGy x 3 # Point A and 3) Total Dose = 8000 cGy in Point A.

Radiotherapy was delivered by Cobalt-60 beam using teletherapy Theratron 780 E or Equinox 80 machine. Brachytherapy was delivered with Micro selectron remote after loading machine high dose rate having Iridium 192 source, using Fletcher-Williamson applicator consisting of an intrauterine tandem and vaginal colpostats.

Concurrent Chemotherapy Protocol Schedule

Premedication with Inj. dexamethasone 8 mg IV, Inj. omeprazole 20 mg IV, Inj. Ondansetron 8mg IV and Inj. Pheniramine maleate 25 mg were given, with adequate hydration for 2 h before and after the chemotherapy.

Control group: Cisplatin 40 mg/m² weekly

In the control group, patients received weekly Cisplatin 40 mg/m² IV in 300 ml normal saline over 1 hour.

Study group: Tab. Erlotinib 150 mg PO OD plus Inj. Cisplatin 40mg/m² weekly

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/m² IV in 300 ml normal saline over 1 hour was started from day 1 of radiation.

Patients (in both control and study group) receiving CCRT were assessed weekly for symptomatic, clinical improvement, and adverse reactions patients were evaluated at the end of treatment completion and during monthly follow-up visits.

Parameters evaluated

The tumor response in both the groups was evaluated using the WHO criteria. The response outcomes assessed included CR, partial response (PR), progression of disease, and stable disease based on clinical and radiological examination. The treatment induced toxicity such as anaemia, leucopenia and nausea/vomiting were graded as per WHO criteria. Skin reaction, diarrhea and genitourinary toxicity were graded as per RTOG criteria.

Statistical Analysis

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

Results

The mean age at presentation in study group and control group was 51.5 years and 53.4 years respectively. Overall 65% patients were from rural areas while 35% of the patients were from urban background.

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

Characteristics	Erlotinib plus concurrer CRT (study group=30)	Concurrent CRT (control group=30)
Age group in years (%)		
31-40	4(13)	5(17)
41-50	9(30)	10(33)
51-60	10(33)	6(20)
≥61	7(24)	9(30)
Performance status (%)		
KPS 70	3(10)	2(8)
KPS 80	25(84)	26(85)
KPS 90	2(6)	2(7)
Smoker (%)		
Yes	6(20)	5(15)
No	24(80)	25(84)
Socioeconomic status		
Lower	25(84)	26(87)
Middle	5(16)	4(13)
Menopausal status		
Premenopausal	11(37)	12(40)
Postmenopausal	19(63)	18(60)
FIGO disease stage (%)		
IIB	21(70)	19(64)
IIIA	4(14)	1(3)
IIIB	5(16)	10(33)

Tumor response

Primary Tumor Control at the End of Treatment
Overall, complete response was seen in 93% in study group and 86% in control group at the end of treatment. In stage IIB and IIIA, complete response was observed in 100% of patients in the

study and control group. Sixty percent patients with stage IIIB achieved complete response in both the groups. Even though results were better in group I but the difference was not statically significant. Table-2 shows the primary tumor control at the end of treatment.

Table 2: Primary Tumor Control at the End of Treatment

		IIB	IIIA	IIIB	Total
Study Group n(%)	Total patients	21 (100)	4 (100)	5 (100)	30 (100)
	Complete Response (CR)	21 (100)	4 (100)	3 (60)	28 (93)
	Partial Response (PR)	0	0	2 (40)	2 (7)
Control Group n(%)	Total patients	19 (100)	1 (100)	10 (100)	30 (100)
	Complete Response (CR)	19 (100)	1 (100)	6 (60)	26 (86)
	Partial Response (PR)	0	0	4 (40)	4 (14)

Stage IIB (CR): Chi square value, $X^2=0.026$ p =0.872 (not significant)

Stage IIIA (CR): Chi square value, $X^2=1.749$ p =0.186 (not significant)

Stage IIIB (CR): Chi square value, $X^2=1.484$ p =0.223 (not significant)

Disease Status at Last Follow Up

Follow up period was 6 to 16 months and median follow up of patients was 10.1 months in study

group and 11.8 months in control group. At the end of follow up, 93% patients in study group and 80% patients in control group were observed to be free of disease. Even though response was better in study group but the difference in two groups was not statistically significant. Table-3 shows disease status at the last follow up.

Table 3: Disease status at last follow up

	Study Group n(%)	Control Group n(%)
No Evidence Of Disease	28 (93)	24 (80)
Residual	2 (7)	3 (10)
Local Recurrence	0	0
Distant Recurrence	0	3 (10)

Chi square value, $X^2=3.508$
 p =0.173 (not significant)

Safety and toxicity

Most common toxicities observed in both the groups with significant difference were nausea, vomiting and diarrhea. In study group, Grade II and III nausea / vomiting was seen in 15 (50%) and 7 (23%) patients respectively. Ten (33%) and 1 (3%) patients were found to have grade II and III nausea/vomiting control group. Grade II and III diarrhea was seen in 9 (30%) and 18 (60%) patients in study group, whereas only 6 (20%) and 1 (3%) patients in control group experienced grade II and III diarrhea.

	Toxicity	Grade I n (%)	Grade II n (%)	Grade III n (%)	Grade IV n (%)	Total No. of Patients (%)
Study Group	Cutaneous Toxicity	9 (30)	12 (40)	9 (30)	0	30 (100)
	Mucosal Toxicity	8 (26)	11 (37)	11 (37)	0	30
	Diarrhea	3(10)	9 (30)	18 (60)	0	30 (100)
	Nausea/Vomiting	6 (20)	15 (50)	7 (23)	0	28 (93)
	Anaemia	6 (20)	16 (53)	2 (7)	0	24 (80)
	Leucopenia	7 (23)	0	0	0	7 (23)
	Frequency of micturition/Urgency	14 (47)	1 (3)	0	0	15 (50)
	Erlotinib induced Skin Reaction	6 (20)	4 (13)	0	0	10(33)
	Control Group	Cutaneous Toxicity	9 (30)	14 (47)	7 (23)	0
Mucosal Toxicity		9 (30)	13 (43)	8 (27)	0	30 (100)
Diarrhea		18 (60)	6 (20)	1 (3)	0	25 (83)
Nausea/Vomiting		17 (57)	10 (33)	1 (3)	0	28 (93)
Anaemia		7 (23)	20 (67)	0	0	27 (90)
Leucopenia		6 (20)	0	0	0	6 (20)
Frequency of micturition/Urgency		15 (50)	0	0	0	15 (50)

Cutaneous toxicity, Chi square- 0.404, P-value=0.817 (not significant)
 Mucosal toxicity, Chi square- 0.699, P-value=0.705 (not significant)
 Diarrhea, Chi square-26.28, P-value=<0.001 (significant)
 Nausea/Vomiting, Chi square-10.76, P-value=0.005(significant)
 Anemia, Chi square-2.353, P-value=0.308 (not significant)
 Leucopenia, Chi square-0.077, P-value=0.782 (not significant)
 Frequency of micturition/Urgency, Chi square-1.034, P-value=0.309 (not significant)

Discussion

Concomitant chemoradiation with weekly cisplatin is standard of care in locally advanced carcinoma of cervix. Adding cisplatin based chemotherapy to radiotherapy provides an additional 30-50% decrease in mortality.¹⁶ A meta-analysis reported that chemoradiotherapy leads to

6% improvement in 5-year survival when compared with radiotherapy alone.⁵ However despite the use of concomitant chemoradiation with cisplatin in locally advanced carcinoma cervix, many patients have experienced locoregional failure (20-25%) and distant failure (10-20%).⁶ The Cochrane meta- analysis showed that the advantage of concomitant chemoradiation

decreases as the stage increases. These facts have stimulated an interest in exploring other concurrent combinations with potentially more aggressive therapy with improved clinical effects. Targeted therapy is the most investigated among them all.^{17,18}

EGFR is a membrane tyrosine kinase expressed by most epithelial cells. Although EGFR is expressed in non-malignant cells, high or abnormal EGFR expressions were found in solid tumors like brain glioma, esophageal cancer, gastric cancer, breast cancer, lung cancer, ovarian cancer and carcinoma cervix. Activation of EGFR is associated with enhanced processes responsible for tumor growth and progression, including the promotion of proliferation, angiogenesis, and invasion or metastasis, and inhibition of apoptosis. So EGFR overexpression is found to be associated with poor response to treatment, disease progression, and poor survival.^{7,8,9}

Erlotinib is an oral and well-tolerated drug which acts by competing reversibly with ATP for binding to the tyrosine kinase domain of EGFR. It inhibits clonal growth, stimulates apoptosis, and induced premature senescence in HPV E6/E7 expressing cervical cells.¹² Erlotinib induces p27KIP1 up-regulation and growth arrest in G phase of cell cycle. It does not stimulate apoptosis in normal cervical epithelial cells. It has been approved by FDA for the treatment of advanced pancreatic cancer with gemcitabine and for treatment of recurrent non-small cell lung carcinoma.^{19,20}

A phase I trial was conducted from December 2004 to August 2006 at Instituto Nacional de Cancer to determine the maximum tolerated dose and related toxicity of erlotinib when administered concurrently with standard chemoradiation in stage IIB to IIIB squamous cell carcinoma cervix. It was composed of 3 cohorts of patients receiving erlotinib in incremental 50, 100, and 150 mg doses. Dose of radiotherapy and cisplatin were fixed. Erlotinib was started one week before starting chemoradiation to allow stable blood levels and was continued daily until the last day of

brachytherapy. Out of 12 evaluable patients, 11 i.e. 91.7% experienced complete response and 1 (8.3%) partial response at the end of treatment. Two out of 12 patients had disease progression after 12 months of follow-up. Maximum tolerated dose was 150 mg. The most common adverse effect was skin rash but no dose interruption was necessary.¹³

Phase II trial was conducted in which Erlotinib was used along with concomitant chemoradiation with weekly cisplatin for locally advanced carcinoma cervix. Patients with stage IIB-IIIB squamous cell carcinoma cervix were included in the trial. Patients were given tablet erlotinib in daily doses of 150 mg. The regimen was started 1 week before starting cisplatin based chemoradiation to achieve stable blood levels and was continued till the last day of brachytherapy. Chemotherapy with cisplatin was started concurrently with radiotherapy, it was administered on day 1, 8, 15, 22, and 29 during teletherapy in a dose of 40 mg/m². Radiotherapy was given over a 9-week period and was conducted in 2 phases: teletherapy a 4500 centigrays divided into 25 daily fractions for 5 days per week, followed by 4 brachytherapy cycles at 1-week intervals using 600 cGy dose prescribed under point A. Thirty four out of thirty six patients with locally advanced carcinoma cervix (94.4%), 11.5 % of whom had bilateral stage IIIB disease, achieved a CR, which was translated into cumulative survival rate of 91.4% with median follow-up of 24 months. The most common adverse effects noticed were skin rash, diarrhea, and nausea, which were grade 1 or 2 in majority of the patients.¹⁴

In study conducted by Rawat et al, 60 locally advanced carcinoma cervix patients received concomitant chemoradiation with and without Erlotinib (150 mg OD PO). Treatment with CRT included cisplatin 40 mg/m² intravenously weekly concurrently with external beam radiation which was followed by intracavitary brachytherapy. WHO criteria was used to evaluate tumor response. Toxicity and adverse events (AEs) were

assessed as per CTCAE v 3. More 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%), which was statistically significant. The adverse effects commonly seen in both the treatment groups were majority of Grade I/II. A higher incidence of diarrhea and skin reaction was noted in the Erlotinib plus CRT group as compared to CRT, whereas the incidence of nausea and vomiting was higher in the CRT group. No Grades IV and V toxicity was observed in Erlotinib with CRT. Erlotinib was observed to be safe with manageable toxicity profile.¹⁵

Erlotinib was tried as a single agent therapy in patients with recurrent squamous cell carcinoma cervix who had progression free survival of at least 6 months. Twenty-eight patients with squamous cell carcinoma were enrolled onto this trial. Twenty-five patients were evaluable. There were no objective responses with four (16%) achieving stable disease; only one patient had a PFS \geq 6 months (4%). The one-sided 90% confidence interval (CI) for response was 0.0%–8.8%. The two-sided 90% CI for the proportion of patients surviving progression-free for at least 6 months is 0.2%–17.6%. Erlotinib was well tolerated with the most common drug-related adverse events being gastrointestinal toxicities, fatigue and rash.²¹

In the study we conducted, overall complete response was seen in 93% in study group and 86% in control group at the end of treatment. At the end of follow up, 93% patients in study group and 80% patients in control group were observed to be free of disease. Difference in two groups was not statistically significant.

Many patients in both the groups experienced grade II and III cutaneous toxicity, mucosal toxicity, nausea / vomiting and diarrhea. Nausea/vomiting and diarrhea being more common in study group and the difference being statistically significant. None of the patients were observed to have grade IV toxicities.

Conclusion

Addition of Erlotinib to standard cisplatin-based CCRT showed improved tumor response in comparison to cisplatin-based CCRT alone in treatment of locally advanced carcinoma cervix, although not statistically significant with manageable toxicity. Small sample size and short follow up period are two limitations of this study. Data on long term safety and survival benefits needs to be explored further.

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