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The Comparative Studyin Locally Advanced Carcinoma Cervix with Radiotherapy and Concurrent Weekly Cisplatin versus Concurrent Daily Erlotinib& Weekly Cisplatin An Extended Follow Up Study.

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Abstract:
Background:*carcinoma cervix is number one malignancy in Indian rural scenario. No one study demonstrate good survival out come till now. Erlotinib is an oral EGFR tyrosine kinase (TK) inhibitor. Early phase clinical trials of Erotinib in combination with cisplatin-based concurrent chemoradiotherapy in locally advanced carcinoma cervix have demonstrated improved antitumour responses with mild toxicity profile However, evidence available on this is limited. We prospectively evaluated the efficacy and safety of Erlotinib (150 mg/day) with concurrent chemo-radiotherapy (CRT) in locally advanced carcinoma cervix and compared with standard CRT.at the time of completion of treatment and then up to 24 months. This study is a follow up of the cases in our previous study "Comparative Evaluation of Radiotherapy with Concurrent Weekly Cisplatin versus Concurrent Daily Erlotinib and Weekly Cisplatin in Locally Advanced Carcinoma Cervix" by the same authors in international journal of scientific study published in January 2018*
This was 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 WHO criteria. Toxicity and adverse events (AEs) were assessed as per CTCAE v 3. In that study we get the higher number of patients achieved 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 (23). The adverse events commonly encountered 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 in comparison CRT, whereas the incidence of nausea and vomiting was higher in the CRT group. grade IV and V toxicity were not observed in study as well as control group . Erlotinib was well tolerated with minimal toxicities . The median duration of therapy was 81 days and than we did follow up, the period of followup up to 24 month . 1 year and 2 year overall survival rate 96.6. % (1 year) 93.3 % (2 year)and progression free survival rates were 90% (1 year) and 83.3 % (2 year) in Erlotinib plus CRT group whereas in control arm overall survival rate were 93.3 % (1 year) and 83.3 % (2 year) and progression free survival rates were 63.3 % (1 year) ,53.3 % (2 year)

Keywords: *Erlotinib, Cervix, Advanced, Carcinoma, Squamous Cell, EGFR, Tyrosine kinase inhibitor, Extended follow-up*

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I. Introduction

cervical cancer is the fourth most common cancer in women, with an estimated 560,505 new cases and 284,923 deaths in 2015. [1] In developing countries cervical cancer is a big health care burden and causes significant morbidity and mortality in women suffering from it . [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] In Indian set up managing cervical cancer is difficult owing to higher stages of malignancy at the time of presentation[,4,5,6]

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 domain that modulates multiple functions, including cell differentiation, growth, gene expression, and development. The EGFR is frequently over expressed 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 intra-cellular catalytic domain of EGFR tyrosine kinase, thereby reversibly blocking EGFR phosphorylation, the signal transduction events and tumorigenic effects associated with EGFR activation. [12] Phase I & II trials of Erotinib in combination with cisplatin-based concurrent chemoradiotherapy in locally advanced carcinoma cervix have demonstrated improved antitumour responses with manageable mild toxicity profile (diarrhoea and rash).[12,13]

In the phase II trial, majority (94.4%) patients on Erotinib 150 mg/day in combination with concurrent chemoradiotherapy 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.[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 concurrent chemo-radiotherapy in patients with locally advanced carcinoma cervix and compared with the concurrent chemo-radiotherapy alone.*These study published in jan 2018 ininternational journal of scientific study as titeld "Comparative Evaluation of Radiotherapy with Concurrent Weekly Cisplatin versus Concurrent Daily Erlotinib and Weekly Cisplatin in Locally Advanced Carcinoma Cervix" by the same authors,* now subsequently followed up for 2 years till December 2017 to assess overall survival , disease free survival and late toxicities in both groups .

II. Material And Methods

This was an open labeled, prospective, comparative study carried out in patients with carcinoma of the cervix, attending Government Cancer Hospital, NetajiSubhash Chandra Bose Medical College Jabalpur (India) during the period of 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 (FIGO) stage IB2-IVA, 3) Age 18–80 years, 4) Eastern Cooperative Oncology Group 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, USG abdomen and pelvis, abdominal and pelvic CT/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 concurrent chemoradiotherapy (CRT) treatment, while the control group received concurrent chemoradiotherapy only.

In the control arm, patients received cisplatin 40 mg/m2 intravenously weekly concurrently with external beam radiation (EBRT). Patients in the study arm received daily Erlotinib 150mg plus cisplatin 40 mg/m2 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 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:1) Control Group: Cisplatin 40mg/m2 IV weekly (Ceiling dose 70 mg) - In the control group, patients received weekly Cisplatin 40 mg/m2 IV in 300ml Normal Saline over one hour. Premedication with Dexamethasone 8 mg, Omeprazole 20mg and 5-HT3 antagonist as antiemetic was given, with adequate hydration for two hours before and after the chemotherapy.

2) Test Group: Daily Erlotinib 150mg OD plus Cisplatin 40mg/m2 IV weekly (Ceiling dose 70 mg) - In the test group, patients received daily tablet Erlotinib 150mg OD before food, and were started one week

before radiation to achieve a stable blood level and were continued until the last day of irradiation. Along with this, weekly Cisplatin 40 mg/m2 IV in 300ml normal saline was started from day 1 of radiation.

Patients (in both control & 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& 6th month 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 complete response (CR), partial response (PR, progression of disease (PD), and stable disease (SD) based on CT/MRI findings. Adverse Events were assessed and graded by Common Toxicity Criteria for Adverse Events (version 3.0) and RTOG/EORTC acute radiation criteria.

Endpoints and Assessments: The primary endpoint was the overall response rate,defined by the percentage of patients who achieved a complete response (CR) or a partial response (PR)according to the Response Evaluation Criteria in SolidTumors (RECIST; version 1.0). Secondary endpointsincluded progression-free survival (PFS), overall survival (OS), and the safety and tolerability of the combinedtherapy. Statistical Analysis:Statistical analysis was performed with software (SPSS, version 19). Descriptive statistics was used to express the data. For categorical variables, Chi square or Fischer exact test were used as appropriate. P values ≤ 0.05 was considered to indicate a statistically significant differencePFS and OS distribution in the current study were described using Kaplan-Meier plots and median estimates.

III. Results

Patients were collected from 2014 to 2015, and a total of 60 patients of locally advanced carcinoma cervix were enrolled in this comparative study. Thirty 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 (23). Tumor response: We observed that higher number of patients achieved complete response (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) (23) .Follow up: The median duration of therapy was 81 days and the follow up period of the study was 24 month . 1 year and 2 year overall survival rate were96.6. % , 93.3 % respectively and progression free survival rates were 90% (1 year) and 83.3 % (2 year) in Erlotinib plus CRT group whereas in control arm overall survival rate were 93.3 % and 83.3 % ate the end of first and second year and progression free survival rates were 63.3 % at the end of 1 year and 53.3 % at the end of 2 years. our study suggests that overall survival and progression free survival both were higher for erlotinib plus CRT arm .(table 7 , table 8) Safety and toxicity: All adverse events commonly encountered in both the treatment groups were of grade I /II /III. A higher incidence of skin reaction (Table 3) (23) and diarrhea (Table 4)(23) 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. (Table 5 & 6) (23)Only less than 10% of cases in either of the groups developed urinary tract infections. No grade IV and V toxicity were observed in Erlotinib with CRT group. Erlotinib was observed to be safe with manageable toxicity profile.

IV. Figures And Tables.

Table 1. Patient's characteristics

Characteristics		Erlotinib plus Concurrent chemoradiotherapy **(Study group= 30)**	Concurrent chemoradiotherapy **(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)
Socio-economic 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	3 cycles	0 (0)	4 (13.3)

total completed	4 cycles	2 (6.7)	9 (30)
	5 cycles	28 (93.3)	17 (56.7)

[1]. Drshyamji Rawat et al , international journal of scientific study 10.17354/ijss/2018/11 . Jan 2018

Table 2: Response to treatment

Response to treatment	**Erlotinib plus Concurrent chemoradiotherapy Number (%)**	**Concurrent chemoradiotherapy Number (%)**	**Chi square value**	**P value**
Complete response (CR)	28 (93.3%)	21 (70%)	5.45	<0.05
Partial response (PR)	2 (6.7%)	9 (30%)		
Total	30	30		

[1]. Drshyamji Rawat et al , international journal of scientific study 10.17354/ijss/2018/11 . Jan 2018

Table 3: Incidence of Skin reaction in the Test group and Control group during treatment period

Adverse Events-Skin reaction	Erlotinib plus Concurrent chemoradiotherapy **(Study group= 30)**		Concurrent chemoradiotherapy **(Control group=30)**	
	Number of patients (%)		Number of patients (%)	
Skin reaction (treatment week)	**Grade 1**	**Grade 2**	**Grade 1**	**Grade 2**
1st**week**	0	0	0	0
2nd**week**	0	0	0	0
3rd**week**	4 (13.3%)	0	2 (6.7 %)	0
4th**week**	16 (53.3%)	3 (10.0%)	2 (6.7%)	1 (3.3%)
5th**week**	20 (66.7%)	6 (20.0%)	5 (16.7%)	1 (3.3%)
6th**week**	25 (83.3%)	4 (13.3%)	5 (16.7%)	0
7th**week**	27 (6.7%)	3 (93.3%)	5 (16.7%)	0

[1]. Drshyamji Rawat et al , international journal of scientific study 10.17354/ijss/2018/11 . Jan 2018

Table 4: Incidence of Diarrhea in the Test group and Control group during treatment period

Adverse Events-Diarrhea	Erlotinib plus Concurrent chemoradiotherapy **(Study group= 30)**			Concurrent chemoradiotherapy **(Control group=30)**		
	Number of patients (%)			Number of patients (%)		
Diarrhea (treatment week)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
1st**week**	13 (43.3%)	14 (46.7%)	0	1 (3.3%)	0	0
2nd**week**	15 (50%)	8 (26.7%)	6 (20%)	3 (10%)	0	0
3rd**week**	5 (16.7%)	4 (13.3%)	8 (26.7%)	3 (10%)	1 (3.3%)	0
4th**week**	5 (16.7%)	1 (3.3%)	0	3 (10%)	3 (10%)	0
5th**week**	1 (3.3%)	0	0	5 (16.7%)	2 (6.7%)	0
6th**week**	1 (3.3%)	0	0	2 (6.7%)	0	0
7th**week**	0	1 (3.3%)	0	1 (3.3%)	0	0

[1]. Drshyamji Rawat et al , international journal of scientific study 10.17354/ijss/2018/11 . Jan 2018

Table 5: Incidence of Nausea in the Test group and Control group during treatment period

Adverse Events-Nausea	Erlotinib plus Concurrent chemoradiotherapy **(Study group= 30)**			Concurrent chemoradiotherapy **(Control group=30)**		
	Number of patients (%)			Number of patients (%)		
Nausea (treatment week)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
1st**week**	0	0	0	0	0	0
2nd**week**	4 (13.3%)	0	0	2 (6.7%)	0	0
3rd**week**	3 (10%)	2 (6.7%)	1 (3.3%)	6 (20%)	3 (10%)	5 (16.7%)
4th**week**	3 (10%)	2 (6.7%)	0	5 (16.7%)	4 (13.3%)	5 (16.7%)
5th**week**	3 (10%)	1 (3.3%)	0	5 (16.7%)	3 (10%)	2 (6.7%)
6th**week**	5 (16.7%)	0	0	5 (16.7%)	4 (13.3%)	1 (3.3%)
7th**week**	2 (6.7%)	0	0	7 (23.3%)	3 (10%)	0

[1]. Drshyamji Rawat et al , international journal of scientific study 10.17354/ijss/2018/11 . Jan 2018

Table 6: Incidence of Vomiting in the Test group and Control group group during treatment period

Adverse Events-Vomiting	Erlotinib plus Concurrent chemoradiotherapy **(Study group= 30)**			Concurrent chemoradiotherapy **(Control group=30)**		
	Number of patients (%)			Number of patients (%)		
Nausea (treatment week)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 1**	**Grade 2**	**Grade 3**
1st**week**	0	0	0	2 (10%)	2 (6.7%)	0
2nd**week**	4 (13.3%)	0	0	4 (13.3%)	2 (6.7%)	2 (6.7%)
3rd**week**	3 (10%)	2 (6.7%)	1 (3.3%)	6 (20%)	3 (10%)	5 (16.7%)
4th**week**	3 (10%)	2 (6.7%)	0	4 (13.3%)	3 (10%)	5 (16.7%)
5th**week**	3 (10%)	1 (3.3%)	0	5 (16.7%)	3 (10%)	2 (6.7%)
6th**week**	5 (16.7%)	0	0	5 (16.7%)	4 (13.3%)	1 (3.3%)
7th**week**	2 (6.7%)	0	0	7 (23.3%)	3 (10%)	0

[1]. Drshyamji Rawat et al , international journal of scientific study 10.17354/ijss/2018/11 . Jan 2018

Table 7: Survival analysis

Table 7.1: Overall survival

	1 YEAR	2 YEAR
ERLOTINIB + CRT	96.6 %	93.3 %
CRT	93.3 %	83 %

Table 7.2: Disease free survival

	1 YEAR	2 YEAR
ERLOTINIB + CRT	90 %	63.3 %
CRT	83.3 %	53.3 %

V. Discussion And Conclusion

The present comparative study indicate that addition of Erlotinib to concurrent chemoradiotherapy, results in improved tumor response compared to concurrent chemoradiotherapy 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 intracavitary brachytherapy (ICBT), and finally to concurrent chemoradiation (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 (NCI) issued a clinical alert to establish CCRT as the standard treatment for carcinoma cervix.[9,14] Cisplatin-based chemoradiation 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.

Epidermal growth factor receptor (EGFR) is frequently overexpressed in 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 tyrosine kinase (TK) inhibitor that reversibly competes with ATP for binding the tyrosine kinase 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 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. Clinical trials have demonstrated encouraging antitumor activity alone or in combination with chemotherapy and exhibited radiosensitizing effects in a variety of malignancies.[17,18,19,20] Early phase clinical trials of Erotinib in combination with cisplatin-based concurrent chemoradiotherapy in locally advanced carcinoma cervix have demonstrated improved antitumour responses with manageable mild toxicity profile (diarrhoea and rash, with no haematological side effects).[12,13]Based upon the promising antitumour outcomes document in early phase clinical trials,[12,13] the present study evaluated the safety andefficacy of cisplatin-based concurrent chemoradiotherapy with or without daily Erlotinib in locally advanced carcinoma cervix in India. In the present comparative study, we found that addition of Erotinib to the concurrent chemoradiotherapy resulted in improved tumour response rate than concurrent chemoradiotherapy alone in locally advanced squamous cell

cervical cancer. The higher number of patients achieved complete response (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 chemoradiotherapy 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/m2, weekly, 5 cycles) and radiotherapy (external beam 4,500 cGy in 25 fractions, followed by 4 fractions/600 cGy/weekly of brachytherapy. Out of 12 evaluable patients, 11 (91.7%) experienced a complete response and 1 (8.3%) partial response at the end of combined treatment. Two of 12 patients have had disease progression after 12 months of follow-up. The most common adverse events noted were skin rash followed by diarrhea, which were manageable. Most of the adverse events 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 dose of Erlotinib that could be given along with cisplatin-based concurrent chemoradiation was 150mg. The addition of Erlotinib to cisplatin-based concurrent chemoradiation 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 chemoradiation in locally advanced (stage IIB to IIIB) cervical cancer. Patients received erlotinib at a dose of 150 mg/day 1 week before and in combination with cisplatin (40 mg/m2 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 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. The most common adverse events 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 were no therapy related deaths reported. The combination of Erlotinib dose of 150 mg/day in combination with cisplatin-based chemoradiation 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 adverse events commonly encountered in both the treatment groups were majority of grade I /II. 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 patents developed skin reaction during the 3rd or 4th week of treatment. The reactions that occurred in the field of irradiation were mostly desquammous type, and were associated with severe itching. It was managed by oral anti histamines, topical emollients and gentian violet. The desquamation subsided by the end of irradiation and new epidermal layer had formed by the second 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 I diarrhea in the first and second week of treatment in Erlotinib group and was managed by adequate hydration, anti- motility drug and probiotics. Only less than 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 grade IV and V toxicity were observed in Erlotinib with CRT group. The adverse events 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.

During follow up of the study it was found that patients in Erlotinib plus CRT group had higher overall survival rate and disease free survival rate at the end of 2 years our findings correlates with the findings of study Phase 2 Trial of Erlotinib Combined With Cisplatin and Radiotherapy in Patients With Locally Advanced Cervical cancer conducted by Angelica Nogueira-Rodrigues et al 22

Summary, cisplatin-based concurrent chemo-radiotherapy when given Along with erlotinib showed improved tumor response in comparison to cisplatin-based concurrent chemo-radiotherapy alone in locally advanced carcinoma cervix patients without producing additional toxicity. In the follow up done for two years better Results we're seen in terms of increased overall survival and progression free survival of patients receiving erlotinib along with standard CRT . Although robust multicentre, randomized control trials with larger sample size are needed to validate these interesting results.

The study had limitations; the sample size was small, conducted at 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.

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