Original Article

Phase 2 Trial of Erlotinib Combined With Cisplatin and Radiotherapy in Patients With Locally Advanced Cervical Cancer

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BACKGROUND: Cisplatin-based chemoradiation (CRT) is the standard treatment for patients with locally advanced cervical cancer. Epidermal growth factor receptor (EGFR) is frequently overexpressed in cervical cancer, and EGFR inhibition itself has antitumor effects and potentiates CRT. Results of a previous phase 1 trial of the EGFR inhibitor erlotinib combined with cisplatin-based CRT (E + CRT) recommended a phase 2 erlotinib dose of 150 mg/day. **METHODS:** Eligibility criteria included International Federation of Gynecology and Obstetrics stage IIB to IIIB epidermoid cervical cancer, no prior therapy, and an Eastern Cooperative Oncology Group performance status of 0 to 2. 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). **RESULTS:** A total of 36 patients completed treatment with E + 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. **CONCLUSIONS:** Treatment with E + CRT appears to be safe and exerts significant activity against locally advanced cervical cancer. To the best of the authors' knowledge, this is the first study to date to demonstrate that a target agent has promising activity against locally advanced cervical cancer. ***Cancer*** **2014;120:1187–93.** *© 2014 American Cancer Society.*

KEYWORDS: cervical cancer, erlotinib, radiotherapy, chemotherapy, clinical trial, phase 2.

INTRODUCTION

Nearly 500,000 new cases of cervical cancer are reported worldwide each year,[1] making it the third most common cancer diagnosed among females. Considering that human papillomavirus (HPV)-associated tumors arise years, if not decades, after an initial infection; screening programs are not widely available; and the currently existing vaccines have no therapeutic efficacy, no measurable decline in HPV-associated tumors is expected before 2040.[2] Therefore, developing novel therapeutic approaches to treat cervical cancer remains of critical importance.

Although cervical cancer is often curable if detected early, a significant number of patients present with locally advanced cervical cancer at the time of diagnosis, a clinical scenario associated with suboptimal therapeutic benefit. Patients with stage III and IVA tumors have 5-year survival rates of 40% and 15%, respectively. For these patients, the initial therapy by far offers the best chance of cure. Conversely, persistent or recurrent disease carries a poor prognosis and leads to death in $>$ 85% of patients.[3] Cisplatin-based chemoradiation (CRT) has been considered the standard care for patients with locally advanced cervical cancer.[4] However, to the best of our knowledge, there has been a dearth of clinical trials since the late 1990s, when a spate of studies in the United States reported the benefits of CRT, and the cure rates for locally advanced cervical cancer have reached a plateau. Furthermore, a recent attempt to combine platinum doublets with radiotherapy reportedly led to high toxicity, thereby limiting its wide implementation.[5,6] Therefore, future advancements in the treatment of locally advanced cervical cancer might rely on more effective and better-tolerated therapies, among which targeted agents are an attractive option.

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.[7] Erlotinib, an EGFR tyrosine kinase inhibitor

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(TKI), has demonstrated encouraging antitumor activity alone or in combination with chemotherapy and has exhibited radiosensitizing effects in a variety of malignancies.[8-11] The combination of erlotinib, radiotherapy, and cisplatin has been tested previously in patients with head and neck cancer, and an acceptable toxicity profile has been reported.[12]

On the basis of the need to improve the therapeutic results for locally advanced cervical cancer, we developed a regimen comprising erlotinib combined with cisplatin and pelvic radiotherapy (E + CRT) and evaluated its safety and antitumor activity. We first performed a phase 1 trial that demonstrated that E + CRT was safe and well tolerated among patients with locally advanced cervical cancer and defined the recommended phase 2 dosage of erlotinib as 150 mg/day.[13] Furthermore, promising antitumor activity also was observed. These findings provided the foundation for the current phase 2 trial.

MATERIALS AND METHODS

Patients

Patients with squamous cell carcinoma of International Federation of Gynecology and Obstetrics stage IIB to IIIB, a bidimensionally measurable lesion, an age of 18 to 70 years, and an Eastern Cooperative Oncology Group performance status of 0 to 2 were considered eligible. For patients of reproductive age, serum negativity for β-human chorionic gonadotropin was essential. Exclusion included the following: neutrophil count < 1500 cells/mm^3, hemoglobin < 10 mg/L, platelet count $< 100{,}000$/mm^3, creatinine > 1.3 mg% or estimated creatinine clearance < 60 mL/minute, total bilirubin ≥ 1.5 mg/dL, alkaline phosphatase higher than normal limits, and calcium ≥ 12 mg/dL despite bisphosphonate therapy. In addition, the following patients also were excluded: those diagnosed with malignancy over the previous 5 years and those with positive paraaortic lymph nodes on computed tomography (CT), uncontrolled infections, psychiatric disorders, cardiovascular disease precluding rapid hydration, collagenosis, and/or known human immunodeficiency virus infection.

All patients provided written informed consent before participation. The study was approved by the Institutional Review Board and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

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 Solid Tumors (RECIST; version 1.0). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and the safety and tolerability of the combined therapy.

Before enrollment, all the patients provided a complete medical history and underwent physical examination, a complete blood count with differential, electrolyte assessment, liver and renal function tests, chest radiography, electrocardiography, abdominopelvic CT, pelvic magnetic resonance imaging, and cystoscopy. In addition, a day before initiating erlotinib therapy, positron emission tomography/CT was performed. Patients were followed weekly during CRT. Toxicity was monitored by obtaining a history and performing physical examination and laboratory assessments. Adverse events (AEs) were classified according to version 2.0 of the National Cancer Institute Common Toxicity Criteria. Follow-up was initiated 1 month after the completion of brachytherapy and was conducted every 3 months for 2 years, followed by every 6 months for the next 3 years. Clinical and gynecological examinations, pelvic magnetic resonance imaging, and abdominopelvic CT were performed at each visit for assessment of disease and late toxicity. Response was assessed on the basis of RECIST and positron emission tomography/CT findings 90 days after the completion of therapy.

Study Design and Therapy

The current study was a nonrandomized, open-label, single-institutional, phase 2 trial of E + CRT for the treatment of locally advanced cervical cancer.

Erlotinib

Patients were treated with oral erlotinib in daily doses of 150 mg. The regimen was initiated 1 week before cisplatin-based CRT to achieve stable blood levels and continued until the last day of brachytherapy. Erlotinib was supplied by Roche Pharmaceuticals (Basel, Switzerland).

Chemotherapy

Chemotherapy was initiated concurrently with radiotherapy, and comprised intravenous cisplatin doses of 40 mg/m^2 (maximum dose, 70 mg), which were administered on days 1, 8, 15, 22, and 29 during teletherapy.

Radiotherapy

Radiotherapy was delivered over a 9-week period and was conducted in 2 phases: teletherapy at 4500 centigrays

TABLE 1. Baseline Patient Characteristics

Characteristic	No. of patients N = 38
Age, y	
Median	44
Range	27-68
ECOG PS, %	
0	52.6
1	44.7
2	2.6
FIGO stage of disease, %	
IIB	57.9
IIIA	2.6
IIIB	39.5
Tumor grade, %	
1	5.3
2	76.3
3	18.4

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics.

(cGy) divided into 25 daily fractions for 5 days per week, followed by 4 brachytherapy cycles at 1-week intervals using a 600-centigrays dose prescribed under point A (International Commission on Radiation Units Report 38), as previously described.[13]

Statistical Analysis

A Fleming single-stage phase 2 trial design was used to test whether there was sufficient evidence to determine that the CR rate was at least 90% (warranting an additional study) versus 75% (clinically inactive). An overall sample size of 34 eligible and assessable patients was targeted. Assuming a 15% loss, 41 patients were required to be included. This design yielded 90% power at a 0.05% level of significance to detect a 90% CR rate.

PFS and OS distribution in the current study were described using Kaplan-Meier plots and median estimates.

The safety population included all the assigned patients who received at least 1 study medication dose, whereas the efficacy population included all the assigned patients who completed the proposed protocol. Summary statistics and frequency tables were used to summarize baseline patient characteristics and rates of AEs, which were reported as maximum severity per patient and type across all therapy cycles.

RESULTS

Patient Characteristics

From February 2006 to June 2008, 41 patients were enrolled, including 8 assessable patients who received the recommended phase 2 dose during the phase 1 part of the trial. However, 5 patients were excluded, 3 of whom had incorrect disease staging and 2 of whom did not complete the protocol as detailed below. Therefore, 38 patients were evaluated for toxicity and 36 for response. The demographic characteristics of these patients are depicted in Table 1. The median age of the patients was 44 years (range, 27 years-68 years). Stage IIB disease was detected in 57.9% of patients, stage IIIA disease in 2.6% of patients, and stage IIIB disease in 39.5% of patients. Approximately 11.5% of patients had bilateral stage IIIB disease. The Eastern Cooperative Oncology Group performance status was 0 in 52.6% of patients, 1 in 44.7% of patients, and 2 in 2.6% of patients. The median duration of therapy for patients who completed therapy was 77 days (range, 64 days-129 days).

TABLE 2. Incidence of Most Frequent Acute Adverse Events Possibly Related to Therapy[a]

	Grade 1/2	Grade 3	Grade 4
Rash	33 (86.8%)	5 (13.2%)	0
Diarrhea	30 (78.9%)	3 (7.8%)	0
Hematological toxicity	19 (50%)	3 (7.8%)	1 (2.6%)
Vascular toxicity	0	2 (5.2%)	0
Radiodermatitis	24 (63.2%)	0	0
Liver toxicity	0	0	1 (2.6%)
Serum creatinine increase	2 (5.2%)	0	0
Nausea	32 (84.2%)	1 (2.6%)	0
Vomiting	18 (47.3%)	1 (2.6%)	0

[a] Adverse events were classified according to version 2.0 of the National Cancer Institute Common Toxicity Criteria.

Toxicity

Therapeutic safety was descriptively analyzed (Table 2) in all 38 patients. The most common AEs were skin rash, diarrhea, and nausea, which were grade 1 or 2 in the majority of patients. Overall, grade 3 toxicities included rash in 5 patients, diarrhea in 3 patients, hematological toxicity in 3 patients, vascular toxicity in 2 patients, nausea in 1 patient, and vomiting in 1 patient. It is interesting to note that E + CRT did not lead to limiting in-field toxicity, and there were no therapy-related deaths reported. Three of the 38 patients (7.9%) experienced grade 3 or 4 late-onset complications: 1 patient developed grade 3 actinic rectitis and 2 patients developed vaginal and small bowel fistulae. No patient experienced grade 3 or 4 bladder complications. However, 2 patients, both of whom were treated in the last cohort of the phase 1 trial, did not complete the planned schedule because they developed Raynaud syndrome and hepatotoxicity, respectively, as previously reported.[13] It is interesting to note that both patients achieved a CR with no further grade 4 toxicity.

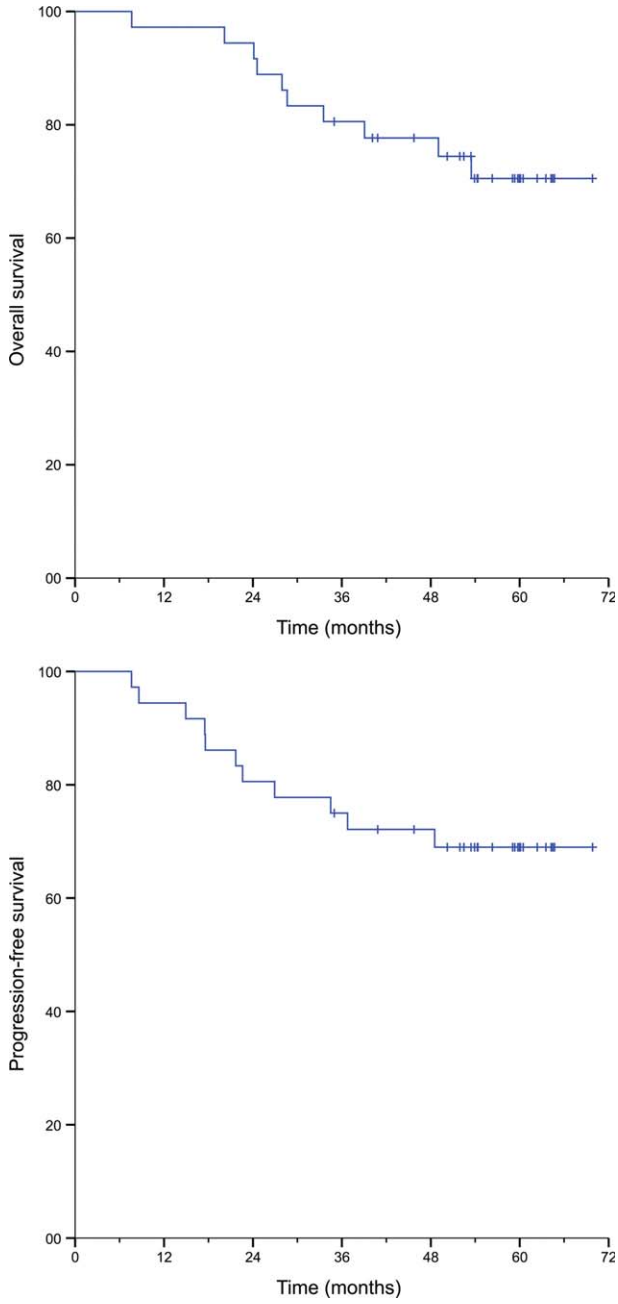

Figure 1. Kaplan-Meier plots for overall and progression-free survival in the 36 patients evaluated for efficacy are shown.

Patient Response

The activity of E + CRT was analyzed in 36 patients, all of whom achieved an objective response by the end of therapy. Thirty-four patients (94.4%; 95% confidence interval, 79.9%-99.0%) achieved a CR, whereas 2 patients (5.6%) achieved a PR. With regard to disease recurrence, 6 patients (16.7%) presented with pelvic failure and 4 patients (11.1%) presented with distant metastases, 3 of whom presented with lung metastases. At a median follow-up of 59.3 months (95% confidence interval, 53.8%-64.9), the median PFS and OS rates were 69.4% and 72.2%, respectively. The 12-month, 24-month, and 36-month cumulative OS rates were 97.2%, 91.7%, and 79.9%, respectively, whereas the cumulative PFS rates were 94.4%, 80.6%, and 73.8%, respectively. Figure 1 presents the Kaplan-

TABLE 3. Historical Database of the Outcomes of Cisplatin-Based Chemoradiotherapy for Locally Advanced Cervical Cancer

Study	No. of Patients	Phase	RR	2-Year PFS	2-Year OS
Whitney 1999[15]	388	3	NR	66%	71%
Rose 1999[18]	526	3	NR	67%	72%
Morris 1999[16]	403	3	NR	76%	81%
Pearcey 2002[17]	253	3	NR	76%	80%
Current study	36	2	94.4%	80.6%	91.4%

Abbreviations: NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate.

Meier estimates of PFS and OS for the study population.

DISCUSSION

In the current study, we report the results of our phase 2 trial of E + CRT for the treatment of locally advanced cervical cancer. In keeping with data from our previous phase 1 study,[13] this combination presented a favorable toxicity profile in addition to promising antitumor activity.

It is interesting to note that 34 of 36 patients with locally advanced cervical cancer (94.4%), 11.5% of whom had bilateral stage IIIB disease, achieved a CR, which translated into a cumulative survival rate of 91.4% with a median follow-up of 24 months. This correlation between response and survival is in keeping with the results of previous reports that promoted CR as a good surrogate for survival from cervical cancer.[14] However, response rates have not been reported in the majority of trials of combined CRT for cervical cancer.[15-18] With regard to PFS and OS parameters, according to data presented by Whitney et al, at a median follow-up of 24 months, 71% of patients with locally advanced cervical cancer were alive, and 66% of the patients treated with cisplatin and radiotherapy were free of disease recurrence.[15] Furthermore, data from Morris et al, Pearcey et al, and Rose et al demonstrated PFS rates of 67%, 76%, and 76%, and OS rates of 72%, 81%, and 80%, respectively.[16-18] In view of this historical database (Table 3),[15-18] the results of the current study reinforce the potential of the current combination therapy to extend survival in patients with locally advanced cervical cancer despite the inherent limitations of comparisons across different clinical trials.

The increase in antitumor activity was not achieved at the expense of toxicity. Assuming that radiodermatitis and diarrhea are the main AEs of conventional pelvic CRT and that erlotinib is a radiosensitizer,[10-12] in-field toxicity was a major concern at the beginning of this trial. However, treatment with E + CRT did not lead to limiting radiodermatitis or diarrhea.

Concomitant cisplatin-based chemotherapy confers an additional 30% to 50% decrease in mortality risk among patients with locally advanced cervical cancer who are undergoing radiotherapy, thus being considered the standard of care for the disease.[4] Nevertheless, this approach has reached a plateau, and novel strategies are therefore warranted. A recent study to explore the synergistic activity of gemcitabine with cisplatin-based CRT revealed that compared with standard therapy, additional chemotherapy improved survival outcomes, although at the expense of increased toxicity, discontinuation of therapy, and patient deaths.[5,6] In short, the rational design of locally advanced cervical cancer studies must avoid the incremental toxicity characteristic of intensified concurrent cytotoxic therapy. Conversely, targeted agents present an attractive option because of their radiosensitizing effects. Nevertheless, more rational approaches attributed to our better understanding of the biological mechanisms underlying the disease[19] should not be disregarded.

The high efficacy rate observed in the current phase 2 trial might be related to the potential role of the EGFR pathway in the carcinogenesis of cervical cancer; this finding is supported by extensive evidence. Nearly 80% of cases of epidermoid cervical cancer express EGFR, with overexpression reported in 20% of cases.[20] EGFR has been validated as an important therapeutic target in patients with head and neck cancer, and assessment of its expression may be a useful prognostic marker in conjunction with HPV status.[21,22] In trials of patients with advanced oropharyngeal cancer, low EGFR and high p16 (or high HPV titer) expression were markers of a good response to treatment and outcome, whereas high EGFR expression was associated with a poor outcome.[21,22]

EGFR has been implicated in radioresistance,[23] and preclinical and clinical data have indicated that EGFR inhibitors can work as radiosensitizers to improve local tumor control further compared with that achieved by

irradiation alone in different disease models,[10,11] including cervical cancer.[24] Several mechanisms contribute to this phenomenon, including cancer stem cell death by EGFR inhibitors, cellular radiosensitization through modified signal transduction, DNA repair inhibition, improved reoxygenation during fractionated radiotherapy, and decreased cell repopulation.[11] One study suggested that clinically significant cell repopulation occurs predominantly in tumors overexpressing EGFR,[25] such as cervical cancer. Moreover, G_1 arrest, mediated by EGFR inhibitors, together with G_2/M arrest, mediated by ionizing radiation, might result in cell-cycle checkpoint deregulation, thereby increasing apoptosis per se.[26] In addition, this selectively sensitizes cells to DNA-damaging agents such as cisplatin. These mechanisms collectively might account for the high antitumor activity observed during the current phase 2 trial.

The radiosensitizing effects might explain the discrepancy between the findings of the current study and the lack of an objective response reported in patients with advanced cervical cancer receiving erlotinib therapy alone[27] or other EGFR inhibitors as well, including gefitinib and cetuximab. It is important to note that prior therapy (radiotherapy, chemotherapy, or surgery) might impact the response to EGFR inhibitors or compromise drug delivery. Prior cisplatin administration substantially decreases erlotinib sensitivity, as indicated by a decreased time to disease progression and the more rapid acquisition of TKI resistance.[28] In addition, targeting EGFR with erlotinib or gefitinib has resulted in modest clinical responses,[29] excluding a select population of patients with non-small cell lung cancer and EGFR TKI domain mutations. In contrast, erlotinib has demonstrated promising activity in patients with vulvar malignancy (another HPV-dependent disease), in which no activating mutations have been identified. This suggests a mechanism for erlotinib response that is different from that observed in patients with non-small cell lung cancer.[9] This should be further explored using a more detailed analysis of patients with cervical cancer as well as patients with other HPV-related tumors. With regard to HPV status and response to EGFR inhibitors in patients with head and neck cancer, some controversies remain,[30-33] and more data are required. Although high-risk HPV types are present in virtually 100% of patients with cervical cancer, to the best of our knowledge this issue has not been addressed to date. In conclusion, at present, there is no argument to support the use of EGFR inhibitors according to HPV status outside a clinical trial.

The combination of chemotherapy and EGFR inhibitors, without radiotherapy, did not demonstrate promising results in patients with advanced, persistent, or recurrent cervical cancer. In a phase 2 trial, the combination of cetuximab with cisplatin was found to be adequately tolerated but did not indicate any additional benefit beyond that of cisplatin therapy.[34] In another phase 2 trial, the combination of cetuximab, cisplatin, and topotecan induced a high rate of serious AEs at the standard dose and schedule and the study was stopped early due to excessive toxicity.[35] The addition of EGFR inhibitors to radiotherapy and cisplatin in patients with locally advanced cervical cancer has been explored in two phase 1 trials. One of the trials demonstrated that the combination of cetuximab, cisplatin, and radiotherapy was feasible, except for patients receiving extended-field radiotherapy.[36] In another trial, our group performed a phase 1 trial of erlotinib combined with CRT and the treatment was found to be safe and well tolerated.[13] Furthermore, promising antitumor activity was observed, reinforcing the development of the current phase 2 study.

In conclusion, the combination of E + CRT is safe and exerts significant activity against locally advanced cervical cancer. To the best of our knowledge, the current study is the first to reveal that a target agent is safe and has promising activity against locally advanced cervical cancer when combined with CRT. Further studies of this combination are warranted and should include the evaluation of other predictive biomarkers as integral components. In this context, a recent study has identified *EGFR* mutations in 36% of cases of squamous cell cervical cancer.[19] However, this observation requires further confirmation and needs to be coupled with a thorough molecular characterization of cervical cancer to implement rational and efficacious targeted therapy for this disease.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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