Phase I Trial of Erlotinib Combined with Cisplatin and Radiotherapy for Patients with Locally Advanced Cervical Squamous Cell Cancer

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Abstract

Purpose: This phase I trial was aimed to determine the maximum tolerated dose and related toxicity of erlotinib (E) when administered concurrently with standard chemoradiation (CRT) for cervical cancer.

Experimental Design: In a modified Fibonacci design, the study aimed to study three cohorts of at least three patients receiving escalating doses of erlotinib (50/100/150 mg) combined with cisplatin (40 mg/m^2, weekly, 5 cycles) and radiotherapy (external beam 4,500 cGy in 25 fractions, followed by 4 fractions/600 cGy/weekly of brachytherapy) in squamous cell cervical carcinoma patients, stage IIB to IIIB.

Results: Fifteen patients were enrolled, 3 at dose level (DL) 50 mg, 4 at DL 100 mg, and 8 at DL 150 mg. Patients presented median age 47 (36-59), stage IIB (46.2%) and IIIB (53.8%). Overall, E+CRT was well-tolerated. Three patients did not complete the planned schedule. One patient at DL 100 mg withdrew informed consent due to grade 2 rash; at DL 150 mg, 1 patient presented Raynaud's Syndrome and had C interrupted, and another patient presented grade 4 hepatotoxicity. The latter was interpreted as dose limiting toxicity and a new cohort of 150 mg was started. No further grade 4 toxicity occurred. Grade 3 toxicity occurred in 6 cases: diarrhea in 3 patients, rash in 2 patients, and leukopenia in 1 patient. E+CRT did not lead to limiting in-field toxicity.

Conclusions: E+CRT is feasible to locally advanced squamous cell cervical cancer and is well tolerated. The maximum tolerated dose has been defined as 150 mg. To the best of our knowledge, this is the first report of a combination of erlotinib, cisplatin, and pelvic radiotherapy.

Worldwide, cervical cancer is the second most common malignancy in women and a major cause of morbidity and mortality (1). The combined treatment involving chemotherapy and radiotherapy has been established as the standard therapeutic approach for patients with locally advanced disease. Several studies have shown the superiority of platinum-based chemotherapy, combined with radiotherapy, when compared with radiotherapy alone (2–8), although some controversy remains (8). Based on these premises, the concomitant administration of radiotherapy plus weekly cisplatin may be considered a reasonable standard of care. However, despite the benefits obtained with the addition of platinum-based chemotherapy, the cure rates of locally advanced squamous cell cervical carcinoma have reached a plateau in recent years. Therapy results are suboptimal; and patients with stage III and IVA tumors have 5-year survival rates of 40% and 15%, respectively (9). There is a clear need to explore new strategies to improve prognosis in this group of patients.

Cancer progression depends largely upon the activity of cell surface membrane receptors that control the intracellular signal transduction pathway. The epithelial growth factor is increasingly important in understanding the malignant process, with prognostic and therapeutic relevance (10). It has been shown that the epidermal growth factor receptor (EGFR) autocrine pathway plays a crucial role in human cancer because it contributes to a number of highly relevant processes in tumor development and progression, including cell proliferation, regulation of apoptotic cell death, angiogenesis, and metastatic spread. Inhibitors of EGFR have been tested in different tumor types with promising results (11–14). Moreover, these compounds were well-tolerated, and few adverse events were observed. We now know that 80% of cervical squamous cell tumors express EGFR, which makes this tumor a candidate for EGFR inhibitor-based therapy (15). Studies combining EGFR inhibitors with chemotherapy and/or radiotherapy have shown that these compounds increase the radiotherapy sensitiveness *in vitro* and *in vivo* in different models (16–20), including cervical cancer.[4]

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Erlotinib is an oral and well-tolerated drug that reversibly binds to the intracellular catalytic domain of EGFR tyrosine kinase, thereby reversibly blocking EGFR phosphorylation, the signal transduction events, and tumorigenic effects associated with EGFR activation. Characteristic toxicities associated with erlotinib include rash, diarrhea, and occasionally, interstitial pneumonitis. Phase I and II studies have shown a good safety profile, tolerability, and encouraging preliminary activity in a variety of solid tumors (21–24). In a multicenter phase II trial, erlotinib was well-tolerated in a heavily pretreated head and neck squamous cell cancer population and produced prolonged disease stabilization (23). In a phase III trial, erlotinib as single drug showed to prolong survival in patients with non–small cell lung cancer after first-line or second-line chemotherapy (14) and the drug is now approved for that indication worldwide. Erlotinib has been tested in combination with gemcitabine in pancreatic cancer and is also approved for that indication in the United States (25). The combination of erlotinib with radiotherapy and cisplatin in locally advanced head and neck cancer showed a high complete response rate with acceptable toxicity (26).

Based on the preclinical data of erlotinib radiosensitization (17–20) and the encouraging results of clinical trials of erlotinib alone or in combination with chemotherapy and radiotherapy in different tumors (14, 23–26), we set out to develop a regimen to evaluate the activity and safety of erlotinib combined with cisplatin and pelvic radiotherapy for locally advanced cervical squamous cell carcinoma. The primary objective of this study was to evaluate the safety and tolerability of the combined treatment and to determine the maximum tolerated dose of erlotinib in this regimen.

Patients and Methods

Eligibility

Patients were required to have histologically proven cervical squamous cell carcinoma stage IIB to IIIB and a bidimensionally measurable lesion. Other eligibility criteria included an age range of 18 to 70 years old, and an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. For women at reproductive age, a serum-negative β-human chorionic gonadotropin assay was required. Exclusion criteria included neutrophils of <1,500 cells/mm^3, hemoglobin of <10 gram/L, platelets of <100,000/mm^3, creatinine of >1.3 mg% or estimated creatinine clearance of <60 mL/min, total bilirubin of ≥1.5 mg/dl, confirmed alkaline phosphatase higher than 136 IU/L, and calcium level of ≥12 mg/dl despite biphosphonates therapy. Additional exclusion criteria were a diagnosis of malignancy in the last 5 y, positive para-aortic lymph nodes in computed tomography (CT), uncontrolled infection, psychiatric disorders, cardiovascular disease precluding rapid hydration, collagenosis, and known HIV infection.

Study design and statistics

This was a phase I, nonrandomized, multicohort, dose escalation study of erlotinib combined with pelvic radiotherapy and cisplatin for locally advanced cervical cancer, conducted at Instituto Nacional de Câncer. In a modified Fibonacci schedule, at least nine patients were included at three dose levels, at a minimum of three patients in each cohort. Dose escalation was not permitted in individual patients.

Toxicity analysis was conducted in all patients included from the beginning of the treatment. Each patient cohort on phase I was followed up during 14 wk (10 wk of treatment and 4 wk of follow-up) before proceeding to a new cohort. The efficacy analysis was conducted with patients submitted to complete protocol. Descriptive statistics on patient characteristics and outcomes were done.

The study was approved by the local Ethics Committee. Subjects gave written informed consent before study entry. The study followed the ethical principles of Good Clinical Practice in accordance with the Declaration of Helsinki.

Pretreatment and follow-up

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, abdominal and pelvic CT, pelvic magnetic resonance imaging, and cystoscopy. One day before starting erlotinib, a positron emission tomography CT was done. Tumor tissue and blood were collected 1 d before and 1 wk after erlotinib alone. Material was obtained according to institutional approved protocols with specific consent in the context of the Brazilian National Tumor and DNA Bank Program. Patients were seen weekly during chemoradiotherapy and brachytherapy. Although on study, patients were clinically assessed for toxicity and complete blood counts weekly. Systemic toxicity from treatment was graded according to the National Cancer Institute common toxicity criteria v2.0. Follow-up visits started 1 month after finishing brachytherapy. Afterwards, this evaluation was done every 3 mo, for 2 y, and every 6 mo, for the following 2 to 5 y. Gynecologic exam, pelvic magnetic resonance imaging, and abdominal and pelvic CT were done at each follow-up visit for tumor response assessment. Objective response was assessed according to Response Evaluation Criteria in Solid Tumors.

Therapeutic plan

The phase I was composed of 3 cohorts of patients receiving erlotinib in incremental 50, 100, and 150 mg doses. The radiotherapy and cisplatin doses were fixed (Fig. 1). Each cohort represented a group of at least 3 patients who were followed up for 14 wk (10 wk of treatment plus 4 wk of toxicity observation). If there was no evidence of limiting toxicity after this period, the study was to progress to the next cohort until the maximum planned dose for erlotinib (150 mg). Dose limiting toxicity (DLT) was defined as a single grade 4 toxicity related to erlotinib use, except rash, or any persisting grade III toxicity. If one patient of three presented limiting toxicity, three additional patients should be included at the same dose level. If two patients presented DLT at the first cohort, the study should be interrupted. If 2 patients presented DLT at dose levels 100 or 150 mg, the maximum tolerated dose should be defined as the previous dose level.

Erlotinib. Patients received erlotinib p.o. daily in doses of 50, 100, or 150 mg, escalated per cohort. Dose escalation was not allowed in individual patients. The drug was started 1 wk before chemoradiation to allow stable blood levels and was continued daily until the last day of brachytherapy (Fig. 1). Erlotinib was supplied by ROCHE Pharmaceuticals.

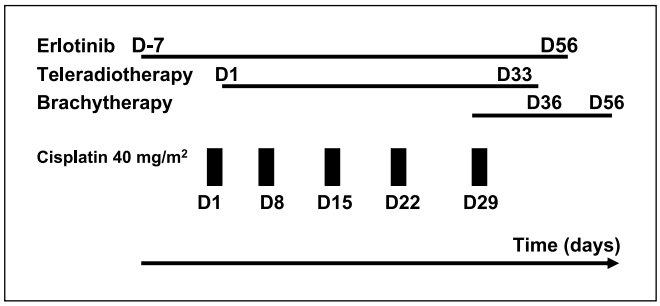

Fig. 1. Erlotinib at the doses of 50, 100, or 150 mg/m^2. Radiotherapy: total 4,500 cGy, (daily fractions of 180 cGy during 5 wk, except weekends). The collection of samples for molecular study was done on D-8 and D1.

Table 1. Main baseline characteristics observed in the 15 patients included in the study

Characteristics	Included patients (n = 15)
Median age, y	47
Eastern Cooperative Oncology Group performance status	%
0	53.8
1	38.5
2	7.7
Stage	%
IIB	46.2
IIIA	0
IIIB	53.8
Tumor grade	%
1	7.7
2	61.5
3	30.8

Chemotherapy. Chemotherapy was started concurrently with radiotherapy, 1 wk after erlotinib initiation. No cisplatin dose escalation occurred. Planned chemotherapy consisted of weekly i.v. cisplatin 40 mg/m ^{2} (70 mg maximum dose) on days 1, 8, 15, 22, and 29 on teletherapy weeks. During the brachytherapy phase, cisplatin was not administered (Fig. 1).

Radiotherapy. The radiotherapy treatment was delivered in no more than a 9-wk interval and was conducted in 2 phases (Fig. 1). Teletherapy at the dose of 4,500 cGy divided into 25 daily fractions, 5 d a week, followed by 4 insertions of brachytherapy with a 1-wk interval among them, using a 600 cGy dose prescribed under point A (ICRU Report 38).

Teletherapy used four isocentric fields (APxPA and LATxLAT), which were planned according to CT and magnetic resonance imaging images by a CT simulator and an image fusion with isocenter, and prescribed high energy photons. Treatment volume was based on ICRU 50 with the gross tumor volume corresponding to the primary tumor measured by the physical and imaging examination. The clinical target volume comprehends the pelvic lymphatic draining evidenced by the paracervical, inner and outer iliac, obturator, presacral, and part of common iliac lymph nodes. The average clinical target volume volumes were the whole uterus, bilateral parametria, presacral nodes, internal and external iliac nodes, uterosacral ligaments, and any other paracervical tissue involved. Field limits were APxPA with upper limit at the L5/S1 joint, lateral limits at 2 cm from the true pelvis and lower limit marked at 3 cm from the lesion inferior limit, including the obturator lymph nodes; LATxLAT followed the same upper and lower limits of the other fields, the anterior limit at the pubic symphysis and the posterior one at the S2/S3 joint, or involving the sacral portion as a whole, according to the gross tumor volume value measured. Reviews were done weekly during the treatment period, performing check films to confirm planned volume. Megavoltage photons energy was used. Planned brachytherapy consisted of high-dose brachytherapy with Iridio 192 afterloading system done in 4 weekly insertions. The first insertion was done on the last teletherapy week, on a day when no teletherapy application was done. Individual planning was designed for each insertion of 600 cGy prescribed at point A, and doses measured in points of interest, as per ICRU Report 38 recommendations.

Dose modification for toxicity. Chemotherapy administration should be based on the hemathologic results. If neutrophils were <1,500/mm^3 and/or platelets were <100,000/mm^3, cisplatin should be withheld. If hemathologic toxicity prevented the treatment administration after a 3-wk interval, this was discontinued and the patient was excluded from the study. If serum creatinine values were above 1.3, cisplatin was delayed for 1 wk and the test was repeated. If these levels persisted for a 2-wk delay period, the patient was excluded from the study. For nausea and vomiting, neuropathy, and ototoxicity, only the cisplatin dose was adjusted. If cisplatin was permanently discontinued, the patient was excluded from the study and continued treatment according to medical decision. If grade 3 or 4 diarrhea occurred, the treatment (cisplatin, radiotherapy, and erlotinib) was discontinued. If this condition persisted after a 2-wk period, the patient was excluded from the study. In the case of grade 4 cutaneous reaction, erlotinib was held for up to 1 wk. If grade 4 skin toxicity was found in the irradiated site, the therapy discontinuation relied on the radiotherapist's discretion.

Results

Patient characteristics. From December 2004 to August 2006, 15 patients presenting histologically proven cervical squamous cell carcinoma stage IIB to IIIB were enrolled onto this study at Instituto Nacional de Câncer.

Fifteen patients were evaluable for toxicity and 12 for response. Demographic characteristics are depicted in Table 1. Patients presented a median age of 47 years (36-59) and 46.2% were staged as IIB, whereas 53.8% were IIIB. Eastern Cooperative Oncology Group performance status was 0 in 53.8% of patients, 1 in 38.5%, and 2 in 7.7%. Within the 12 patients who received through erlotinib + chemoradiation, median duration of treatment and follow-up was 70 (67-80) days and 19 (11-28) months, respectively.

Toxicity. Dose escalation proceeded through cohort 3 (erlotinib, 150 mg). Three patients were enrolled at dose level 50 mg, 4 at dose level 100 mg, and 8 at dose level 150 mg. Three patients did not complete the planned schedule. One patient at dose level 100 mg withdrew informed consent due to grade 2 rash. For this reason, another patient was included at the same dose level. At dose level 150 mg, a patient presented Raynaud's Syndrome after starting chemotherapy. This was interpreted as cisplatin-related toxicity, and she had chemotherapy interrupted but continued on erlotinib and radiotherapy without further toxicity. The third patient that did not complete the planned schedule was also treated in the 150 mg cohort; the patient presented grade 4 hepatotoxicity at the last cycle of chemotherapy; she was also on erythromycin due to skin rash and antiemetics. All medications were interrupted and she fully recovered. The latter was interpreted as DLT and a new cohort of 150 mg was started. No further grade 4 toxicity occurred (Table 2). Four patients were included at this cohort because the last two patients signed informed consent at the same time and both filled all inclusion criteria.

The most common adverse event was skin rash. Thirty-six percent of patients experienced grade 1 rash, 50% experienced grade 2, and 14% grade 3. No dose interruption was necessary.

Table 2. Drug-related toxicity observed in the patients included in the study

Grade	1 and 2	3	4
Leukopenia	2	1	0
Thrombocytopenia	2	0	0
Radiodermitis	5	0	0
Diarrhea	10	3	0
Rash	12	2	0
Liver Toxicity	0	0	1

Table 3. Adverse Events observed in the studied patients according to the respective cohort

Adverse event	Grade	Cohort 1 erlotinib (50 mg) (n = 3)	Cohort 2 erlotinib (100 mg) (n = 4)	Cohort 3 erlotinib (150 mg) (n = 8)	Total (n = 15)
Neutropenia	1	0	0	0	0
	2	1	0	0	1
	3	0	0	0	0
Thrombocytopenia	1	2	0	0	2
	2	0	0	0	0
	3	0	0	0	0
Radiodermitis	1	0	1	0	1
	2	1	0	2	3
	3	0	0	1	1
Diarrhea	1	0	2	2	4
	2	1	2	3	6
	3	1	0	2	3
Rash	1	1	2	2	5
	2	1	2	4	7
	3	0	0	2	2
Liver	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
	4	0	0	1	1

All patients were told to use sunscreen. Some patients were treated with oral erythromycin; however, clinical benefit was limited.

Diarrhea was also a frequent side effect, occurring in 86.7% of patients at any grade. In total, 26.7% of the patients presented diarrhea grade 1; 40% grade 2 and 20% grade 3. Grade 3 diarrhea was limited to 24 hours in all patients. Patients were ambulatorially treated with oral hydration and loperamide; treatment delay was not necessary. Pelvic radiodermitis were present in 33% of the patients, all were either grade 1 or 2.

Hematologic toxicity occurred in 40.2% of the patients. Most of them presented toxicity grades 1 or 2. Only one patient presented leukopenia grade 3.

Overall, grade 3 toxicity occurred in 6 patients: diarrhea in 3 patients, rash in 2 patients, and leukopenia in 1 patient. As mentioned above, 1 patient presented grade 4 hepatotoxicity, but this can be attributed to other drugs in use. It should be highlighted that the combination of erlotinib to chemotherapy and pelvic radiotherapy did not lead to limiting in-field toxicity (radiodermitis, rash, or persisting diarrhea), and there were no treatment-related deaths. There was no treatment break due to toxicity. Adverse events for each cohort are depicted in Table 3.

Response to treatment. Response was evaluated 3 months after the end of treatment. Lesions were measured according to Response Evaluation Criteria in Solid Tumors. Fifteen patients were evaluable for toxicity and 12 for response. Three patients were not considered for response because they did not complete the planned schedule. Out of 12 evaluable patients, 11 (91.7%) experienced 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. At the time of analysis, these two patients had died due to progressive disease.

The three patients who did not complete the planned schedule and were not included for response evaluation presented indeed complete response.

Discussion

Radiotherapy is the primary local treatment for most patients with locally advanced cervical carcinoma. Five-year survival rates of 65% to 75%, 35% to 50%, and 15% to 20% are reported for patients treated with radiotherapy for stage IIB, IIIB, and IV tumors, respectively (9). Concomitant cisplatin-based chemotherapy may confer an additional 30% to 50% reduction in the risk of death from cervical cancer for women with locally advanced disease undergoing radiotherapy (27). Based on the available data, chemoradiotherapy has become the preferred approach for women with locally advanced disease (2–7, 27). However, despite the benefits obtained with the addition of platinum-based chemotherapy, therapy results are suboptimal for stage III and IVA tumors (9). There is a clear need for improvement. Exploring novel strategies based on targeted therapy seems a reasonable approach.

EGFRs are frequently overexpressed in a wide range of human tumors (18). Although receptor activity is tightly controlled in normal cells, the genes encoding these receptors have escaped from their usual intracellular inhibitory mechanisms in malignant cells through amplification, overexpression, or mutation, favoring cell proliferation. For these reasons EGFR is one of the most studied and exploited targets for molecular cancer therapy. Nearly 80% of the cervix uteri squamous cell carcinomas express EGFR, 20% of which shows overexpression (15), making this tumor a natural candidate to be drugged with EGFR inhibitors.

The potential benefits when combining EGFR inhibitors and radiotherapy sparked interest in investigating the combined treatment for cervical cancer. Preclinical and clinical results indicate this group of drugs can work as radiosensitizers, improving local tumor control compared with irradiation alone (16–20). Several mechanisms have been identified to contribute to better tumor control, including direct death of cancer stem cells by EGFR inhibitors, cellular radiosensitization through modified signal transduction, inhibition of

repair of DNA damage, reduced repopulation, and improved reoxygenation during fractionated radiotherapy (19). Moreover, when combining EGFR inhibitor and cytotoxic drugs, the occurrence of cross-resistance is infrequent because the cellular targets and mechanisms of action are different (18). Erlotinib is an orally administered tyrosine kinase inhibitor that specifically targets the EGFR tyrosine kinase domain blocking cell proliferation. In phase I, II, and III trials, erlotinib has a good safety profile and has shown encouraging activity in a variety of solid tumors (14, 22, 28, 29). Also, the combination of erlotinib with chemoradiotherapy as initial treatment for head and neck tumor patients has already been explored. In a phase II trial, patients were treated with erlotinib combined with cisplatin and radiotherapy, with a complete pathologic response in 84% of patients (26).

In this phase I trial, the primary goal was to determine the maximum tolerated dose and the safety of erlotinib when combined with cisplatin and pelvic radiotherapy in locally advanced cervical cancer. Three dose levels of erlotinib were evaluated in combination with standard fixed chemoradiotherapy. As it was the first time erlotinib would be used in addition to pelvic radiation and cisplatin, we preferred not to add another treatment modality simultaneously (brachytherapy to teletherapy, chemotherapy, and erlotinib). Brachytherapy was started after finishing chemoradiation, making it possible to access, separately, if any acute toxicity was due to either teletherapy or complicated by brachytherapy. The radiotherapy regimen encompassed, by this way, 5 weeks of chemoradiation and 4 weeks of brachytherapy. If the treatment was done without interruptions, total time should be, at least, 63 days, same as Morris' and Keys' proposed total time. In our trial, some patients were treated in longer periods due to holiday breaks. There was no treatment delay due to toxicity.

Samples of blood and tumor tissue were collected at 2 different times of the treatment, 1 day before and 1 week after erlotinib alone, aiming future genomic and proteomic studies. Because we intend to perform correlative studies, those samples will be analyzed when the phase II is completed.

The results of this study should be viewed in light of the potential toxicities of this combination. Head and neck cancer patients treated with first line erlotinib combined with cisplatin and radiotherapy presented high incidence of grade III/IV in-field dermatitis (26). Also, an analysis of lung cancer patients treated with erlotinib alone (14) revealed the frequency of diarrhea was significantly increased when compared with placebo (55% versus 19% overall and 6% versus <1% for grade 3 or higher). Assuming that radiodermitis and diarrhea are the main side effects during conventional chemoradiotherapy for cervical cancer (2–8), and that erlotinib is a radiosensitizer (16–20, 26), in-field toxicity was a major concern at the beginning of this trial. However, in the phase I trial reported here, the combination of erlotinib + chemoradiation did not lead to limiting radiodermitis or diarrhea. Most patients presented in-field toxicity grades 1 or 2. Five patients (33%) presented grade 1 or 2 radiodermitis and 10 patients (66%) presented grade 1 or 2 diarrhea. Three patients (20%) presented grade 3 diarrhea—patients met criteria for this graduation due to increase in the number of bowel movements. The episodes were limited to 24 hours, without incontinence, need for parenteral support, or treatment delay. Episodes were well-controlled with loperamide and oral hydration. There was no grade IV diarrhea.

Characteristic toxicities associated with erlotinib and other EGFR inhibitors include a typical rash. All agents targeting the EGFR pathway, including both small molecule tyrosine kinase inhibitors and monoclonal antibodies binding EGFR, are associated with dermatologic toxicity (predominantly dry skin and acneiform rash). This is thought to be due to high levels of EGFR expression in the basal layer of the epidermis (30). The occurrence and severity of rash during treatment may correlate with antitumor efficacy (31). In the phase III trial that led to the approval of erlotinib as an accepted second line treatment for non–small cell lung cancer patients, rash was significantly more common with erlotinib than with placebo (76% versus 17% overall; ref. 14). In this phase I trial, skin rash was also the most common adverse event. However, compared with skin rash observed in trials of erlotinib alone (14), this combined treatment did not increase its severity. Fourteen patients presented skin rash; grade 1 or 2 in 12 patients and grade 3 in only 2 patients. Dose interruption due to skin rash was unnecessary, although one patient withdrew informed consent (skin rash grade 2).

There was a trend for a positive correlation between patients who presented skin rash and diarrhea—77.8% of patients who presented rash grades 2 or 3 also presented grades 2 or 3 diarrhea ($P = 0.085$). The absence of statistical significance may be explained by the small number of patients analyzed in the trial. It was not observed any correlation between more intense skin rash and "in-field" dermatitis. It was also not observed any protective effect in terms of skin rash in the irradiated area compared with circumjacent skin.

One patient treated at dose level 150 mg presented Raynaud's Syndrome after starting chemotherapy. Based on published data of correlation of cisplatin treatment and Raynaud's Syndrome (32), this phenomenon was attributed to the cytotoxic drug. Cisplatin was withdrawn and the patient recovered. She was treated with erlotinib and radiotherapy without further toxicity. No DLT were observed at dose levels 50 and 100 mg. The DLT of acute hepatotoxicity occurred at dose level 150 mg; the patient presented the toxicity at the end of chemotherapy treatment when she was also taking erythromycin and antiemetics. Acute severe hepatitis, though rare, is occasionally observed with EGFR inhibitors gefitinib or erlotinib (33), cisplatin (34), and erythromycin (35). All medications were interrupted and the patient presented complete recovery. The event was considered a DLT and another cohort of 150 mg were initiated. No further limiting toxicity was observed at this dose level, defining 150 mg as the maximum tolerated dose.

This is the first report of an oral tyrosine kinase inhibitor of the EGFR used in combination with pelvic radiotherapy. These results may have implications for the design of trials for other pelvic tumors, for example, squamous cell carcinoma of the anus.

In previous phase III trials of chemotherapy and radiotherapy for cervical carcinoma, pelvic complete response was observed in 38% to 75% of patients (36–39). In this trial, in 12 evaluable patients, 11 (91.7%; 95% confidence interval, 59.8-99.6%) experienced complete response at the end of combine treatment. The three patients not included for response evaluation presented indeed complete response. The safety of

the combination and its response rates must be confirmed in the phase II trial.

Conclusion

The maximum tolerated dose of erlotinib has been defined as 150 mg/day. The addition of erlotinib to standard chemoradiotherapy for locally advanced cervical cancer does not seem to increase in-field or systemic toxicities and the combination is well-tolerated. A phase II trial of this combination is ongoing.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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