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BRIEF REPORT

Effectiveness and safety of erlotinib in 2 patients with carcinoma of the cervix

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KEYWORDS
Erlotinib;
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Compassionate-use;
Effectiveness;
Safety

Abstract
Objective: To assess the effectiveness and safety of the use of erlotinib in the treatment of refractory cervical cancer after retrospective analysis of 2 clinical cases.
Methods: The clinical records were assessed for the patients who started treatment with erlotinib, on a compassionate-use basis, with an oral dosage of 150 mg/day until June 2008. The pharmacy dispensing records were also assessed to evaluate adherence to treatment. Progression-free survival was assessed and adverse reactions were recorded in the medical records.
Results: Three patients with recurrent, advanced cervical cancer were candidates for treatment with erlotinib, 2 of whom were only starting treatment. In both cases, the women had previously received between 3 and 4 different treatment lines. Progression-free survival was 6 months and 4 months in each case. The adverse reactions to the treatment were slight.
Conclusions: Erlotinib presented some similar results to those obtained from cisplatin doublets in women with refractory cervical cancer, with minor adverse effects. However, these results need to be corroborated in the clinical studies field on a wider section of the population.

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PALABRAS CLAVE
Erlotinib;
Carcinoma de cérvix;
Uso compasivo;
Efectividad;
Seguridady

Efectividad y seguridad de erlotinib en 2 pacientes con carcinoma de cérvix uterino

Resumen
Objetivo: Evaluar la efectividad y la seguridad del tratamiento con erlotinib en cáncer de cérvix uterino refractario a través del análisis retrospectivo de 2 casos clínicos.
Métodos: Se revisaron las historias clínicas de las pacientes que iniciaron tratamiento con erlotinib vía oral a dosis de 150 mg/día como uso compasivo hasta junio del 2008, así como los registros de dispensación de farmacia para valorar la adherencia al tratamiento. Se evaluó la supervivencia libre de progresión y se recogieron las reacciones adversas descritas en la historia clínica.
Resultados: Tres pacientes con cáncer de cérvix avanzado recurrente fueron candidatas a tratamiento con erlotinib, 2 de las cuales iniciaron tratamiento. En ambos casos las mujeres habían recibido entre 3 y 4 líneas de tratamiento previas. La supervivencia libre de progresión fue de 6 y 4 meses en cada caso. Las reacciones adversas al tratamiento fueron leves.
Conclusiones: El erlotinib presentó unos resultados similares a los logrados con los dobletes de cisplatino en mujeres con cáncer de cérvix refractario, con leves efectos adversos. Sin embargo, habrá que corroborar estos resultados en el ámbito de los ensayos clínicos con poblaciones más amplias.

Introduction

Cervical cancer is the third most frequently-occurring gynaecological tumour in the world.[1] Sixty-eight percent of cases occur in developing countries, where cervical cancer is the second most common cause of death from cancer in women.

The age at which it appears varies between 50 to 60 years, with a mean of 54 years. Precursor lesions in younger women appear between 24 and 40 years.

It is one of the few tumours which can be detected at an early stage by means of a cost-effective, simple and reliable screening method: the Papanicolaou smear. Early diagnosis of this disease has allowed a reduction in mortality of 70% in the last 40 years; however in developing countries the incidence is increasing due to the lack of these programmes of treatment.

Immunisation against the human papillomavirus (HPV) with the new vaccinations is intended to prevent the persistent infection with certain forms of HPV, and therefore, to reduce the incidence of this type of cancer.[2]

The 80%-90% of cases of cervical cancer are squamous cell carcinomas and, to a lesser degree, adenocarcinomas (10%-15%), adenosquamous (2%-5%), adenoacantomas, embryonal cell carcinomas or hyalines, sarcomas, and others.

Effective treatment in the initial stages of the disease (stages I and II) may result in healing in 80% of women, being reduced to 60% of women at stage III.[3] Erlotinib is an inhibitor of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) used in the treatment of locally advanced or metastatic non-microcytic lung cancer and in metastatic cancer of the pancreas associated with gemcitabine, and which is found in studies in other tumours which are expressed by EGFR, such as cervical cancer.[4]

The objective of this study is the assess the efficacy and safety of erlotinib in the treatment of advanced cervical cancer by reviewing 2 clinical cases.

Methods

A retrospective study was undertaken in which requests for compassionate use of erlotinib until June 2008 were reviewed. Data was collected corresponding to patients to whom treatment with erlotinib was authorised in the context of cervical cancer. The clinical history of the patients was reviewed, gathering the following details: age and sex, diagnosis, stage, previous treatments, dosage instructions, clinical development, and side effects. The dosage of erlotinib used was a continuous oral dosage of

Table 1 RECIST criteria for assessment of the response of solid tumours

Objetive response	
Complete response	All lesions disappeared, confirmed at 4 weeks
Partial response	Reduction by at least 30% of the diameter of the lesion(s), confirmed at 4 weeks
Disease progression	Increase by 20% of the diameter of the lesion(s) or appearance of new lesions
Stable disease	Neither a partial response nor progression

150 mg/day. The pharmacy dispensation records for the medication were reviewed to evaluate adherence to the treatment. The clinical response was evaluated according to the RECIST criteria for complete response, partial response and progression[5] (Table).

Results

Compassionate use of erlotinib for cervical cancer was requested in 3 patients, and was administered in 2 of them; the third patient died before beginning treatment. The age of the patients who received treatment was 64 and 68 years. Prior to treatment with erlotinib the patients had received several courses of treatment, and in both cases the first course of treatment was concurrent cisplatin-radiotherapy.

The first patient was a woman aged 64 years, diagnosed in December 2004 with epidermoid cervical cancer at FIGO stage IIIc. After receiving 5 of the 6 scheduled weekly cycles of concurrent cisplatin-radiotherapy, a non-operable relapse appeared at 10 months in the follow-up period. Subsequently, treatment with topotecan was initiated on days 1, 8, and 15 every 28 days according to the clinical test protocol; after 3 cycles, there was the onset of nodular progression and the patient abandoned the study. She began palliative treatment with paclitaxel-carboplatin every 21 days, showing progression after 3 cycles, after which she received cisplatin on day 1 and topotecan from the first day until the third, of which, in the third cycle, the dosage was reduced by 20% due to mucositis. After 3 cycles of treatment, the onset of progression of the disease occurred.

In October 2007 the determination of the EGFR was requested, to assess the use of erlotinib, which was granted. Compassionate use of erlotinib was requested and once the authorisation was received from the *Agencia Española del Medicamento* (Spanish Medication Agency), the patient began treatment with erlotinib in monotherapy, in December 2007, at a dosage of 150 mg/day, taken orally.

In March 2008 the patient showed a clinical deterioration, and the treatment was temporarily interrupted. After 1 month, the patient showed a clinical improvement and resumed the treatment, showing a grade II cutaneous toxicity.

After 6 months of treatment, the computerised tomography showed a progression of the disease, and the treatment with erlotinib was discontinued. The adherence to the treatment based on the pharmacy dispensation records was 75%. At present, the patient is continuing treatment with intravenous vinorelbine.

The second case was a woman of 68 years, diagnosed in February 2005 with an epidermoid carcinoma of the uterine cervix, FIGO stage IIB. She began weekly treatment with concurrent cisplatin-radiotherapy, of which she received 6 cycles with good tolerance. The patient continued her check-ups, and at 2 years and 4 months the onset of ganglion progression of 3.7 cm occurred, which required ureterohydronephrosis. Treatment with cisplatin-fluorouracil for 4 days was proposed, which the patient accepted; she received 3 cycles, after which the treatment was discontinued due to grade IV gastrointestinal toxicity and ganglion progression. In January 2008, she began treatment with cisplatin day 1 - topotecan days 1, 2, and 3 every 21 days, which was discontinued after the first cycle due to poor tolerance and clinical progression.

In March 2008 an EGFR determination was requested, which had positive results and compassionate use of erlotinib 150 mg/day was requested, which was initiated in April. After 1 month of treatment the patient had grade I acne of the face; she did not experience diarrhoea. Pain appeared in the right lower limb, in the event of the eco-Doppler being carried out, the results of which were normal. The patient continued treatment with erlotinib with a 100% adherence until July 2008, when the patient died. She had attained a survival without progression of 4 months.

Discussion

In the last decade, the role of chemotherapy in women with recurrent or metastatic advanced cervical cancer has been directed towards improving the objective reponse rate and the palliation of symptoms with an acceptable toxicity, with the treatment of choice being cisplatin in monotherapy. The coupling of cisplatin with other agents, such as ifosfamide,[6] paclitaxel,[7] and topotecan,[8] have demonstrated better responses and survival without progression compared with cisplatin in monotherapy (4.6 compared with 3.2 months; 4.8 compared with 2.8 months; 4.6 compared with 2.9 months). However only the cisplatin-topotecan combination has demonstrated an advantage, albeit modest, in total survival (9.4 compared with 6.5 months), situating this association as the treatment of choice.

It is necessary to develop new couplings which do not contain cisplatin for the treatment of women who relapse less than 12 months after receiving chemoradiotherapy based on cisplatin, and to find more effective chemotherapy regimens for the treatment of metastatic cervical cancer.

Studies are just beginning on the role of directed therapy with monoclonal antibodies and small molecules in cervical cancer; its use in controlling cervical cancer, at the moment, is merely speculative. To date, studies on MeSH *erlotinib* and *uterine cervical neoplasm* have not appeared on Medline, although there is another study on other inhibitors of tyrosine kinase, such as gefitinib.[9]

Studies are being developed to clarify the role of erlotinib, an inhibitor of tyrosine kinase, administered orally, in the management of metastatic cervical cancer, which provide objective data surrounding the use of this new molecule *(a phase II evaluation of OSI 774 in the treatment of persistent or recurrent squamous cell carcinoma of the cervix [GOG 0227-D])*.

However, while we await the results of the clinical tests, the compassionate use has provided some experience with the use of erlotinib in controlling the disease, although there are no published data.

In our study, erlotinib was used in women with refractory, recurrent cervical cancer, who received 3-4 courses of treatment. Despite the study only covering 2 cases, it is plausible that erlotinib, at a dosage of 150 mg/day, constitutes an alternative in the control of advanced recurrent cervical cancer with a rate of survival without progression of approximately 5 months, similar to that attained with the cisplatin combinations. The treatment did not have significant adverse effects, only a slight grade I

cutaneous toxicity in one of the patients and grade II in the other.

We look forward to the publication of the results of the clinical tests with erlotinib, which, with a broader population, will allow the efficacy data to be verified, as well as possibly positioning the drug in the treatment of the disease.

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