BLEPHARITIS RELATED TO CETUXIMAB TREATMENT IN AN ADVANCED COLORECTAL CANCER PATIENT

BLEFARITIS ASOCIADA AL TRATAMIENTO CON CETUXIMAB EN ADENOCARCINOMA COLORRECTAL AVANZADO

RAMÍREZ-SORIA MP1, ESPAÑA-GREGORI E2, AVIÑÓ-MARTÍNEZ J3, PASTOR-PASCUAL F1

ABSTRACT

Case report: A 52-year-old woman with advanced colorectal cancer was referred to us for treatment of Cetuximab-related ocular side-effects.

Discussion: Cetuximab is a monoclonal antibody that specifically blocks epidermal growth factor receptor activity. It has recently been approved to treat some tumors such as metastatic colorectal cancer and some ORL cancers. Tolerance to it seems to be better than that to the classic chemotherapeutic agents. However it has several side-effects. Cetuximab-related eyelid toxicity has been recently described, though the pathogenesis has not yet been clearly established (Arch Soc Esp Oftalmol 2008; 83: 665-668).

Key words: Colorectal cancer, monoclonal antibodies, epidermal growth factor receptor, blepharitis.

RESUMEN

Caso clínico: Mujer de 52 años diagnosticada de adenocarcinoma colorrectal, remitida a nuestro servicio por presentar tras iniciar tratamiento con Cetuximab reacción adversa palpebral.

Discusión: El Cetuximab es un anticuerpo monoclonal cuya diana es el receptor del factor de crecimiento epidérmico. Ha sido incorporado recientemente al tratamiento de tumores, principalmente el cáncer colorrectal metastáctico y los tumores del área otorrinolaringológica. Su tolerancia es en principio mejor que la de los agentes quimioterapéicos clásicos. Sin embargo, no está exento de efectos secundarios. La toxicidad palpebral asociada a Cetuximab ha sido recientemente descrita, por lo que la patogenia no está establecida claramente.

Palabras clave: Adenocarcinoma colorrectal, anticuerpos monoclonales, receptor del factor de crecimiento epidérmico, blefaritis.
INTRODUCTION

The application of monoclonal antibodies for the treatment of tumors and other pathologies is increasingly widespread. Cetuximab is a monoclonal antibody targeting the epidermic growth factor receptor (EGFR) utilized for treating tumors expressing this factor. Initially, its toxicity is slight, but new toxic effects may appear. This short paper presents the case of a woman with metastatic colorectal adenocarcinoma with skin and eyelid toxicity associated to Cetuximab.

CASE REPORT

A 52-year-old woman diagnosed with colorectal adenocarcinoma in 2001, treated by means of surgical resection with a negative extension study.

In 2002, after a relapse a new operation was performed and radio chemotherapy was added according to the Mayo Clinic protocol (six chemotherapy cycles with 5 fluorouracil and folicic acid). In 2003 new progression was evidenced, and 11 chemotherapy cycles were applied with irinotecan and 5-fluorouracil (FOLFIRI scheme) (1). In 2005 an abdominal-perineal amputation was performed and 3 cycles of irinotecan and 5-fluorouracil were applied. Through immunohistochemia the EGFR was identified in the primary tumor. It was decided to add Cetuximab to the treatment as it is a specific EGFR monoclonal antibody.

Three weeks later, the patient exhibited a bilateral strange body feeling, and itching in the eyelid edges, photophobia and tearing. Visual acuity, intraocular pressure and eye fundus were normal. An important palpebral erithema was evidenced, with clear cornea free of ulcers or keratitis and moderate conjunctival hyperemia (fig. 1). Immunological, allergic or infectious pathologies were discarded. The symptoms remitted with tobramycine-dexametason eye drops and artificial tears. When beginning a new cycle of chemotherapy, the patient exhibited a reappearance of blepharitis with moderate inflammatory reaction, conjunctival hyperemia, eyelid edges edema, slight scaling, tricomegalia, thickened and twisted eyebrows (fig. 1). Also, she exhibited eczema in forearms and folliculitis in the legs (figs. 2 and 3), xerosis in the lips and slight acne-shaped eruption (figs. 4 and 5). She was referred to dermatology for assessment. The eye
disorder was treated with terramycine cream three times a day for 20 days and, considering the positive result, it was decided to establish it as prophylactic treatment prior to new Cetuximab cycles.

At present, the patient exhibits vaginal tumor infiltration and is awaiting oncological treatment.

**DISCUSSION**

Cetuximab is an IgG1 chimeric monoclonal antibody targeting a receptor of the tirosinkinase HER family, specifically HER 1, c-erb1 or EGFR, with which it has an affinity 10 times higher than with its natural ligand (2).

The drug was utilized for treating tumors such as colorectal metastatic cancer and ENT tumors in combination with chemo- or radio-therapy (3,4). It is utilized with irinotecan in patients with metastatic colorectal cancer EGFR+.

EGFR is involved in the control of cellular survival, the development of the cellular cycle, angiogenesis, cellular migration and metastatic invasion.

Cetuximab prevents the binding of EGFR-endogenous ligands, inhibiting their function. In addition, it induces the internalization of EGFR with a reduction of receptors on the cellular surface. The post-receptor effects of Cetuximab involve protein p27kip1, a negative regulation factor which deactivates cycline-dependent kinase, stopping the cellular cycle in G1 (2). Accordingly, Cetuximab inhibits the proliferation and induces apoptosis of EFGR+ tumor cells. In vitro, Cetuximab inhibits the production of angiogenic factors by tumor cells and prevent the migration of endothelial cells. In vivo, it inhibits the expression of angiogenic factors by tumor cells and reduces neovascularization and metastasis. Cetuximab also directs cyto-toxic immune cells towards EGFR+ tumor cells (cytotoxicity regulated by antibody-dependent cells).

As other monoclonal antibodies, Cetuximab exhibits a different and «more benevolent» toxicity profile than classic chemotherapy agents. Its most common side-effect is skin toxicity, expressed as acneiform rash. However and considering its recent inclusion in the therapeutic arsenal, new toxic effects may appear.

Skin reactions occur in over 80% of patients, of which 15% are severe. These reactions generally appear in the first week of treatment and remit without leaving sequels upon suspension of the treatment. Their main expression is acneiform eruption, seborrheic dermatitis, facial and trunk maculopapular rash, infrequently in limbs (5). Even less frequent are nail disorders such as paronychia. Our patient came to our practice three weeks after beginning treatment for acne, xerosis in lips, blepharitis and eczema in limbs.

Fig. 4: Acne-shaped eruption and serosis in lips.

Fig. 5: Acne-shaped eruption.

As other monoclonal antibodies, Cetuximab exhibits a different and «more benevolent» toxicity profile than classic chemotherapy agents. Its most common side-effect is skin toxicity, expressed as acneiform rash. However and considering its recent inclusion in the therapeutic arsenal, new toxic effects may appear.

Skin reactions occur in over 80% of patients, of which 15% are severe. These reactions generally appear in the first week of treatment and remit without leaving sequels upon suspension of the treatment. Their main expression is acneiform eruption, seborrheic dermatitis, facial and trunk maculopapular rash, infrequently in limbs (5). Even less frequent are nail disorders such as paronychia. Our patient came to our practice three weeks after beginning treatment for acne, xerosis in lips, blepharitis and eczema in limbs.

The pathogeny of skin toxicity could be explained by the inaction of EGFR. However, the pathogeny of the palpebral damage associated to Cetuximab has not been established clearly because it has been described only recently (5). It could be that in the skin Cetuximab would target the EGFR of epidermal sweat glands and the epithelium of the hair follicle while in the eye the target would also be the Meibomium glands which secrete tear lipidic components in a similar way as the sweat glands. Previous experimental studies have pointed to the role of EGFR in the differentiation and the proper development of the hair follicle (2). This would explain the alterations observed in the eyebrows. Likewise, the inaction of EGFR in the Meibomium glands would cause a secretion dysfunction and the alterations of the palpebral edge described above.

ARCH SOC ESP OFTALMOL 2008; 83: 665-668
REFERENCES