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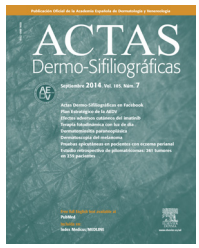

ORIGINAL

Predictors of Tumor Response to Cetuximab and Panitumumab in 116 Patients and a Review of Approaches to Managing Skin Toxicity☆

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Monoclonal antibodies (cetuximab, panitumumab);
Adverse drug reaction;
Rash;
Clinical markers;
Tumor response

Abstract

Background and objectives: Cetuximab and panitumumab are monoclonal antibodies that target the epidermal growth factor receptor (EGFR) in the treatment of metastatic colorectal cancer. Most patients develop a papulopustular rash, which may predict tumor response. We studied whether the other adverse cutaneous effects associated with these monoclonal antibodies are also clinical predictors of response. We also reviewed publications describing approaches to treating the papulopustular rash since no evidence-based guidelines have yet been published.
Material and methods: We performed a retrospective study of 116 patients with metastatic colorectal cancer receiving anti-EGRF therapy with cetuximab or panitumumab at Hospital Universitario Donostia.
Results: In total, 81.9% of the patients developed a papulopustular rash. Patients who received the most cycles of treatment with the EGFR inhibitor were at the highest risk of developing the rash, and these patients also had the most severe rash reactions ($P = .03$). All of the patients who exhibited a complete tumor response had the rash, and the incidence of rash was lower in patients with poor tumor response ($P = .03$). We also observed an association between tumor response and xerosis (53.4% of the patients who developed xerosis also exhibited tumor response, $P = .002$). The papulopustular rash was managed according to an algorithm developed by our department.

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Conclusions: Severe papulopustular rash and xerosis may be clinical predictors of good response to anti-EGFR therapy. Patients who develop a papulopustular rash should be treated promptly because suboptimal treatment of this and other adverse effects can lead to delays in taking the prescribed anti-EGFR dose or to interruption of therapy.

PALABRAS CLAVE
Inhibidores del factor de crecimiento epidérmico;
Anticuerpos monoclonales (cetuximab, panitumumab);
Reacción adversa medicamentosa;
Erupción cutánea;
Marcadores clínicos;
Respuesta tumoral

Factores predictores de respuesta y revisión de la toxicidad cutánea de cetuximab y panitumumab en 116 pacientes

Resumen

Introducción y objetivos: Cetuximab y panitumumab son anticuerpos anti-factor de crecimiento epidérmico (anti-EGFR) usados para el cáncer colorrectal metastásico. La mayoría de los pacientes desarrollan una erupción papulopustulosa que podría predecir la respuesta tumoral. Además, producen otros efectos adversos cutáneos, por lo que hemos estudiado si estos también podrían ser predictores clínicos de respuesta. Así mismo, hemos realizado una revisión del tratamiento de la erupción papulopustulosa, ya que no existen directrices basadas en la evidencia.

Material y métodos: Estudio retrospectivo de 116 pacientes. Se incluyeron pacientes afectos de cáncer colorrectal metastásico en tratamiento con los anticuerpos anti-EGFR, cetuximab o panitumumab, en el Hospital Universitario Donostia.

Resultados: El 81.9% de los pacientes desarrolló la erupción papulopustulosa, siendo el riesgo mayor y de mayor intensidad cuantos más ciclos de anti-EGFR se administraban ($p = 0,03$). Todos los pacientes que obtuvieron una respuesta tumoral completa desarrollaron la erupción. Cuanto peor era la respuesta tumoral, menor era la frecuencia de la erupción ($p = 0,03$). También se encontró una asociación entre la xerosis y la respuesta tumoral (el 53,4% de los que obtuvieron respuesta tumoral desarrollaron xerosis, $p = 0,002$). El manejo de la erupción papulopustulosa se llevó a cabo mediante un algoritmo desarrollado por nuestro servicio.

Conclusiones: En la práctica clínica la erupción papulopustulosa grave y la xerosis pueden ser predictores clínicos de buena respuesta al tratamiento anti-EGFR. Los pacientes con esta erupción deben tratarse precozmente, ya que el tratamiento subóptimo de estos efectos secundarios puede conllevar un retraso en la dosis o su interrupción.

Introduction

Epidermal growth factor receptor inhibitors (EGFR/HER1/Erb1) are antitumor agents that have emerged in recent years to treat advanced-stage solid tumors.[1,2] Inhibition of EGFR-mediated signals is achieved with *1*) monoclonal antibodies, namely cetuximab (Erbitux) and panitumumab (Vectibix), which are used mainly in metastatic colorectal cancer,[1,3] but also in squamous cell carcinoma of the head and neck and skin[2,4] and *2*) low-molecular-weight drugs, namely erlotinib (Tarceva), gefitinib (Iressa), used in lung cancer and pancreatic cancer, and lapatinib (Tykerb), used in breast cancer.[5] These drugs prevent adenosine triphosphate binding to the intracellular portion of EGFR. Unlike conventional chemotherapy, EGFR inhibitors are used at an optimal biological dose to achieve better tolerance.

EGFR is a transmembrane glycoprotein expressed in the skin and in the epithelial cells of 30% to 100% of solid tumors.[2] The activation of EGFR by its growth factor ligands triggers a series of processes that regulate epidermal proliferation, differentiation, apoptosis, migration and synthesis of inflammatory cytokines.[6] EGFR therefore plays a role in the development and normal differentiation of epidermal keratinocytes, stimulating their growth, protecting against UV-induced damage, inhibiting inflammation, and favoring wound healing. By altering keratinocyte proliferation and differentiation, EGFR inhibition exerts an antineoplastic effect, but it also triggers a series of cutaneous toxic effects, such as abnormal follicular keratinization and a secondary inflammatory response.[5,6] All EGFR inhibitors cause dose-dependent cutaneous toxicity.[7]

Adverse cutaneous effects are observed in sites expressing high levels of EGFR, and the most common effect is a papulopustular rash, which occurs in over 80% of patients.[7,8] The rash tends to be mild, but it can be moderate or severe in up to 50% to 60% of cases,[9,10] requiring dose reductions or discontinuation of antitumor treatment. Other adverse effects are paronychia, hair alterations, pruritus, and xerosis.

Research is underway to study markers that help to predict the effectiveness of EGFR inhibitors and avoid unnecessary toxicity by limiting administration to patients who will potentially benefit from them. Activating KRAS and NRAS mutations are currently the only predictors of resistance to approved anti-EGFR inhibitors used in clinical practice, and their evaluation has been included in the