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Combination of an EGFR blocker and a COX-2 inhibitor for the treatment of advanced cutaneous squamous cell carcinoma

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Summary
Cutaneous squamous cell carcinoma (SCC) is one of the most common cancers worldwide. Epidermal growth factor receptor (EGFR) is expressed at the cell surface by more than 90 % of SCCs and its activation is responsible for cell cycle progression, proliferation, survival, angiogenesis and metastasis. Cyclooxygenase-2 (COX-2) is an enzyme up-regulated through EGFR signaling and responsible for some of the EGFR-dependent biological effects. An 88-year-old man presented with a recurrent, locoregionally metastatic SCC of the right parietal region, which was resistant to radiotherapy. With a combination therapy of an EGFR blocker (cetuximab) and a COX-2 inhibitor (celecoxib), the tumor regressed partially and the patient's Karnofsky index improved. We speculate that the combined use of cetuximab and COX-2 inhibitors can be a new and effective therapy for advanced and recurrent cutaneous SCCs.

Keywords
squamous cell carcinoma – EGFR – COX-2 – Cetuximab

Introduction
Cutaneous squamous cell carcinoma SCC is the second most common cancer in whites [1]. In certain clinical settings such as the use of immunosuppressive medications in organ transplant recipients, the risk of developing SCC is increased by 65- to 250-fold [1]. SCCs can be treated either surgically or non-surgically. Non-surgical options include laser, cryotherapy, topical chemotherapy, topical immune response modifiers (e. g. imiquimod), photodynamic therapy (PDT), radiation therapy, and – after metastatic spread – systemic mono- and multiagent chemotherapy [1]. Few therapeutic options are left for advanced or metastatic disease, primarily platinum-containing chemotherapeutic regimens. Advanced SCC often occurs in elderly patients who tolerate systemic chemotherapy poorly; there is a great need for more specifically targeted and safer therapeutic strategies.

Almost all cutaneous SCC express EGFR, which may confer metastatic potential [2]. Stimulation of EGFR by its ligands increases signal transduction leading to activation of genes responsible for the biological effects of EGFR (Figure 1 and [3]). Among the genes with increased expression after EGFR stimulation is cyclooxygenase-2 (COX-2) [4]. COX-2 is responsible for production of prostaglandin E2 (PGE2), which is known to rapidly phosphorylate EGFR and to trigger the MAPK signaling pathway [5]. Pai et al. have demonstrated that the inhibition of matrix metalloproteinases (MMPs), TGF-α or c-Src can block PGE2-mediated EGFR transactivation and downstream signaling. This indicates that PGE2-induced EGFR transactivation involves signaling transduced via TGF-α, an EGFR ligand, probably released from the cell membrane by c-Src-activated MMP(s) (Figure 1 and [6]). Thus, up-regulation of COX-2 expression by EGFR stimulation may establish a vicious cycle (Figure 1) of increased cell proliferation and incomplete cell differentiation. Indeed,

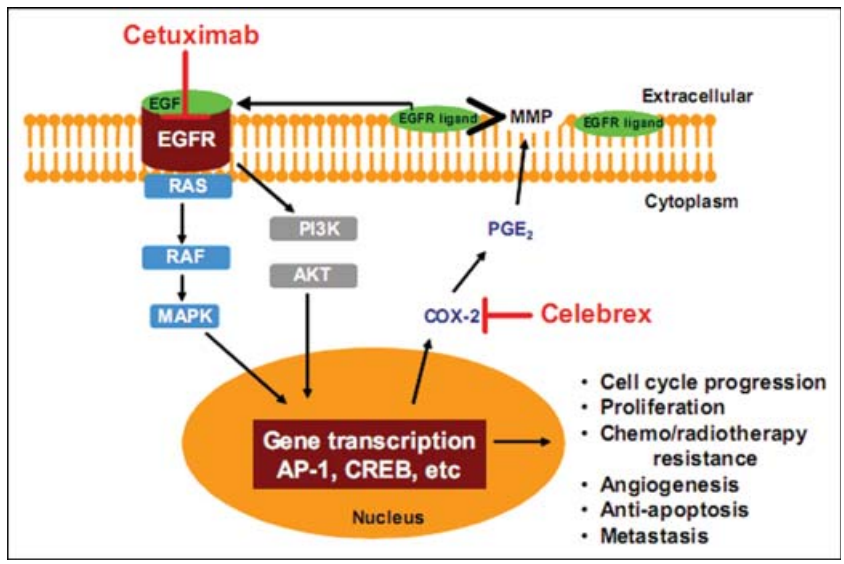

Figure 1: Schematic presentation of the signaling pathways activated by the EGFR stimulation and their biological relevance.

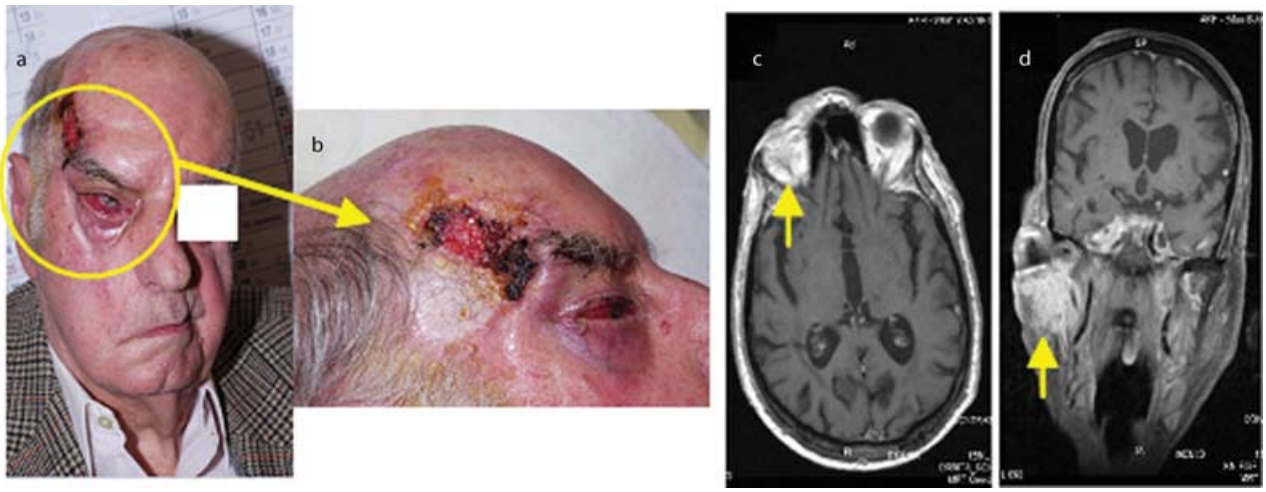

Figure 2: Clinical presentation of the patient at the time of admission. (a, b) The patient presented himself with a hemorrhagic, partially crusted ulcer (histopathology: invasive SCC) with ipsilateral ocular/periorbital redness, severe facial nerve paralysis and two palpable submandibular lymph nodes. (c, d) On the CT scan a 1.4 cm intraorbital tumor mass (c, arrow), a metastatic lesion in right parotid gland (d, arrow) but no distant metastasis could be observed.

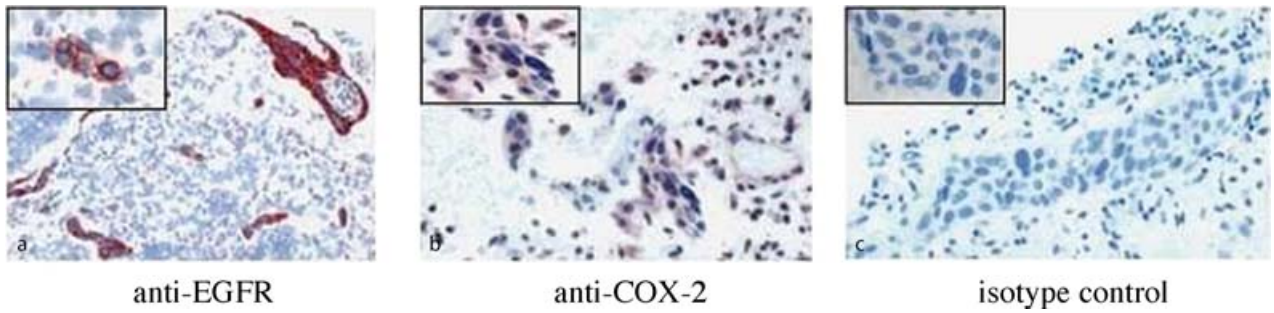

Figure 3: Patient's tumor cells express the EGFR and COX-2. Immunohistochemistry for expression of the EGFR (a, anti-EGFR antibody clone 31G7, Invitrogen) and the COX-2 (b, anti-COX-2 antibody clone SP21, Lab Vision) by patient's tumor cells. No staining with isotype control antibody could be observed (c). 200x and 400x.

combined inhibition of these molecules (EGFR and COX-2) has been shown to be an effective strategy in the treatment of a variety of epithelium-derived tumors including SCC of the head and neck [7].

Case Report

An 88-year-old man presented with a 5 × 10 cm partially hemorrhagic/crusted ulcer on the right parietal region and ipsilateral severe facial nerve paralysis as well as ocular and periorbital erythema (Figure 2). His Karnofsky index was reduced to 60 % [8]. Computed tomography (CT) and ultrasonography showed metastasis of the primary cutaneous SCC into the right orbital cavity, the right parotid gland and the ipsilateral submandibular lymph nodes. The tumor did not penetrate into surrounding bones; distant lesions in thorax or abdomen could not be detected (Figure 2). A biopsy from the border of the tumor revealed an invasive poorly-differentiated (G3) SCC.

The patient informed us that a similar lesion at the same location had been removed by Mohs microsurgery a year previously. He described the recurrence of the erosions, and later, ulcers and progressive worsening of the facial nerve paralysis starting three months after surgery.

Because of the patient's age and his reduced Karnofsky index, we initially chose radiotherapy as a monotherapy and avoided chemotherapy. The patient received 60 Gy over one month to his right parietal and ocular regions. Unfortunately, he developed severe side effects among them radiogenic dysphagia, aspiration pneumonia, candida stomatitis, progressive right exophthalmus and a further reduction of overall physical performance. CT scan of the skull showed progression of intraorbital metastasis and intraorbital bleeding.

Immunohistochemical analysis demonstrated tumor cells expressing both EGFR and COX-2 (Figure 3a, b). Therefore, we chose combination therapy with a monoclonal antibody against EGFR, cetuximab, and a COX-2 inhibitor, celecoxib.

Cetuximab (Erbitux®, Merck KGaA, Germany) a humanized murine monoclonal antibody against EGFR was approved for the treatment of SCC of the head and neck in Switzerland in 2005 and is currently under review by the European Medicines Agency (EMEA) for this indication. It was administered intravenously (i. v). One cycle of therapy consisted of a loading dose of 400 mg/m^2 followed with 250 mg/m^2 weekly dose for 6 weeks [9]. Prior to administration of cetuximab, the patient received i. v anti-histamine (diphenhydramine chloride) as premedication to inhibit possible allergic reactions. Celecoxib (Celebrex®, Pfizer Corporation, Austria), a selective COX-2 inhibitor, was administered at the dose of 100 mg p. o. once daily. The patient received two cycles of cetuximab

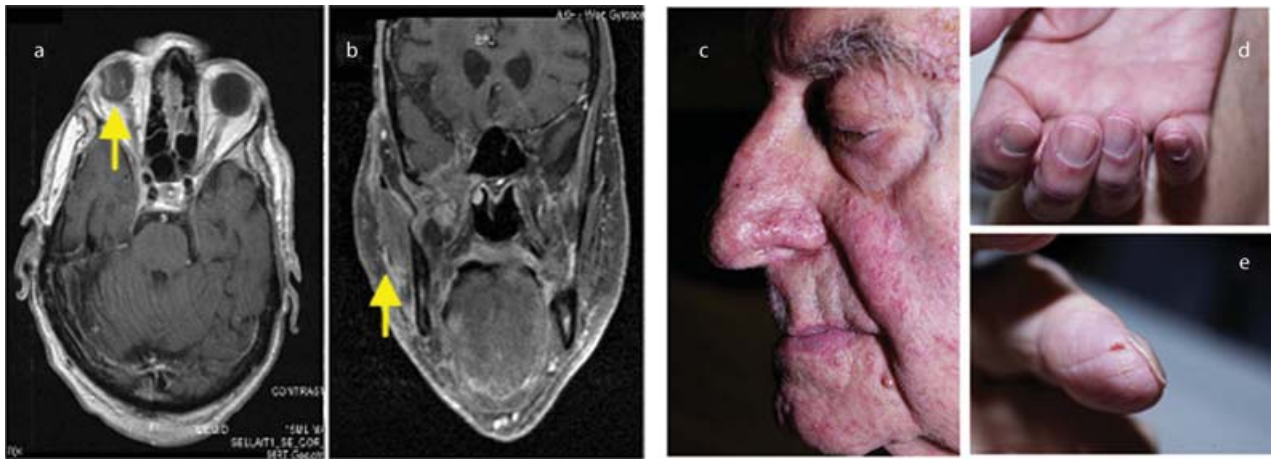

Figure 4: Clinical response to the combination therapy with the cetuximab (Erbitux®) and celecoxib (Celebrex®). CT scans performed at weeks 8 and 16 showed complete remission of the intraorbital (a, arrow) and submandibular metastases at week 8 and partial response of metastasis to the right parotid gland at week 16 (b, arrow). Therapy was associated with cutaneous side effects attributed to cetuximab including follicular-pustular rash (c, known to happen in 70–80 % of patients treated with cetuximab and to correlate with response to therapy), nail disorders (paronychia, d) and skin drying/fissuring (e).

separated by a 2 week pause. Celecoxib was administered continuously.

We performed CT scans of skull, thorax and abdomen a week after completion of each cycle, namely on weeks 8 and 16. Complete regression of the intraorbital as well as the submandibular metastases was observed at week 8 and confirmed at week 16. A partial response of the intraparotid metastasis was observed at week 8 and confirmed at week 16 (Figure 4). There was no further progression of the disease for the next 7 months. The therapy was well tolerated, did not result in any noteworthy laboratory adverse events and was accompanied by considerable improvement of the Karnofsky index to 90 %. According to Response Evaluation Criteria In Solid Tumors (Recist) Guidelines, the patient had experienced partial response to the administered therapy [10].

During the therapy we observed the development of a follicular-pustular rash on the face, back and thorax as well as paronychia, skin drying and fissuring of the hands (Figure 4). These side effects began to develop during the second week of treatment. The follicular-pustular rash could be classified as grade 2 cutaneous reaction [11] and successfully treated with oral tetracycline, while the dryness was treated symptomatically.

Discussion

Molecularly targeted compounds have opened new treatment horizons in oncology [12]. Numerous drugs have been developed which target growth and survival pathways necessary for carcinogenesis. Among them the EGFR signaling pathway deserves particular attention. Its biological importance is evidenced by the appearance of various epidermal defects in mice lacking EGFR in the epidermis [13]. On the other hand, EGFR is over-expressed in cutaneous SCCs and their lymph node metastases [2].

Inhibition of the EGFR signaling cascade is accompanied by a series of dermatological adverse effects [14]. These include among others a follicular-pustular rash (40–100 % of patients), skin drying and fissuring, a nail disorder (paronychia), inflammatory and infectious sequelae such as blepharitis, cheilitis and cellulitis, interstitial lung disease (< 0.5 % of patients), infusion reactions (~ 3 % of patients, 90 % of these after first infusion and manifested as airway obstruction, urticaria and/or hypotension) and hair changes (curlier, finer and more brittle hair on scalp and extremities) [14]. All these adverse events have been attributed to cetuximab treatment and, interestingly, the development of the follicular-pustular rash correlates well with the clinical response to cetuximab [14]. A recent consensus guideline summarizes management strategies for patients developing follicular-pustular rash while receiving EGFR inhibitors [11].

In conclusion, we have described an elderly patient with an invasive cutaneous SCC who could be successfully treated with a combination of cetuximab and celecoxib. The combination therapy was accompanied by minor cutaneous side effects. Therefore we suggest that cetuximab in combination with a selective COX-2 inhibitor can be an effective and well-tolerated treatment regimen for locoregionally advanced cutaneous SCC.

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Conflict of interest

None.

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