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Concomitant cetuximab and radiation therapy: A possible promising strategy for locally advanced inoperable non-melanoma skin carcinomas (Review)

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Abstract. Non-melanoma skin cancers (NMSCs) include a heterogeneous group of malignancies arising from the epidermis, comprising squamous cell carcinoma (SCC), basal cell carcinoma (BCC), Merkel cell carcinoma and more rare entities, including malignant pilomatrixoma and sebaceous gland tumours. The treatment of early disease depends primarily on surgery. In addition, certain patients present with extensive local invasion or metastasis, which renders these tumours surgically unresectable. Improving the outcome of radiotherapy through the use of concurrent systemic therapy has been demonstrated in several locally advanced cancer-treatment paradigms. Recently, agents targeting the human epidermal growth factor receptor (EGFR) have exhibited a consolidated activity in phase II clinical trials and case series reports. Cetuximab is a monoclonal antibody that binds to and completely inhibits the EGFR, which has been revealed to be up-regulated in a variety of SCCs, including NMSCs. The present review aimed to summarize the role of anti-EGFR agents in the predominant types of NMSC, including SCC and BCC, and focuses on the cetuximab-based studies, highlighting the biological rationale of this therapeutic option. In addition, the importance of the association between cetuximab and radiotherapy for locally advanced NMSC is discussed.

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Contents

1. Introduction

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) represent the more frequently occurring non-melanoma skin cancers (NMSCs), which are a group of malignancies arising from the epidermis, also comprising Merkel cell carcinoma and more rare entities, including malignant pilomatrixoma and sebaceous gland tumours. These malignancies are particularly frequent in the United States and geographical areas close to the Equator, including Australia (1). BCC, which originates from the cells composing the basal layer of the epidermis, occurs more frequently than SCC; it also presents a less aggressive behaviour and an improved prognosis. Immunosuppression, sun exposure and certain genetic diseases (e.g., xeroderma pigmentosum and Gorlin syndrome) are the most highly acknowledged risk factors (2). Since the 1960s, the incidence of NMSC worldwide has markedly increased, perhaps due to the progressive decrease in the stratospheric ozone stratum, with a consequent increased exposure to ultraviolet (UV) rays (3).

Early BCC and SCC [T1, with no risk factors (defined as small lesion, G1-2, no perineural invasion, no immunosuppression, no recurrent lesion)], may be treated effectively with surgery alone. The most frequently used surgical technique is Mohs micrographic surgery, which consists of the removal and extemporaneous analysis of every skin stratum until disease-free margins are identified. Excision of lesions with postoperative assessment of their margins is also

widely employed, being less expensive compared with Mohs surgery and equally as efficacious as far as small tumours are concerned (4). Skin tumours that are locally advanced and/or have a high risk of recurrence (comprising T >1 mass, invasion of perineural spaces, poor differentiation grade and spread to lymph nodes) may be treated with Mohs surgery combined (or not) with lymph-node dissection and/or adjuvant radiotherapy and chemotherapy combined (chemoradiotherapy) (5,6).

Locally advanced SCCs that are medically inoperable or surgically non-resectable have a poor prognosis, although occasionally they may be cured with radiotherapy alone, or with chemoradiotherapy. In clinical trials, the combination of cisplatin and radiotherapy has yielded an improved outcome compared with radiotherapy alone, and this combination is the standard of care for non-resectable or inoperable SCC and BCC (7). Recurrent or metastatic diseases, which are more commonly observed in SCC compared with BCC, have a grim prognosis, and often are treated with systemic therapy. Systemic therapies that have been used in advanced NMSC include cytotoxic chemotherapy, immunotherapy and molecularly targeted agents (8-11), including bleomycin, 5-fluorouracil, 13-*cis*-retinoic acid, cisplatin, doxorubicin, interferon-α 2a, gefitinib, cetuximab, capecitabine and erlotinib.

2. Biology of NMSC and the rationale for using targeted therapy

UV light exerts a fundamental role in the initiation and promotion of the carcinogenesis of NMSC, provoking the accumulation of genetic changes, which alter several oncogene-mediated pathways and, ultimately, lead to a selective growth advantage (5). One of these disrupted pathways is the epidermal growth factor receptor (EGFR) pathway. EGFRs are a family of tyrosine kinase transmembrane receptors, which include four different proteins, namely EGFR (or HER-1), c-erBB2 (or HER-2), ErbB-3 (or HER-3) and ErbB-4 (or HER-4) (12,13). Activation of EGFR, which normally is exerted by several extracellular soluble ligands, including EGF, results in autophosphorylation of the receptor's intracellular domains. This autophosphorylation leads to the activation of downstream effectors, including Ras and PI3K (phosphoinositide 3-kinase). The Ras- and the PI3K-stimulated pathways are able to elicit cell proliferation, activation of angiogenesis and inhibition of apoptosis (14,15). EGFR is normally expressed in human cells, but higher levels of expression have been identified in numerous malignancies, including NMSCs (16). In previous studies [e.g., (17,18)], particularly those employing immunohistochemical staining, ~90% of the incidences of SCC and 60% of BCCs exhibited an overexpression of EGFR. The overexpression of EGFR is associated with poor prognosis in solid tumours, particularly SCC of the head and neck, and the degree of EGFR expression may correlate with the response to radiation therapy (19,20). A severe overexpression of EGFR may correspond with a wide expression of receptors on the cell surface, leading to a constitutive activation of the downstream effectors, with generation of a marked, proliferative ligand-mediated signal. In fact, a specific clinical study has demonstrated a positive correlation between the intensity of EGFR expression and the nuclear proliferative index, Ki-67, in head-and-neck SCC (21). Tumour cells increase their proliferative activity, and the repopulation effect derived from this mechanism may counteract the effects of radiotherapy (22,23). The predominant EGFR downstream effector is the G-protein, Ras. Ras is tethered to cell membranes, and is activated by tyrosine kinase receptors, including EGFR (15). In several solid tumours, a DNA mutation of the *ras* gene is present, and this often leads to constitutive activation of Ras protein. This last step often leads to resistance to EGFR inhibitor drugs, including cetuximab, panitumumab, gefitinib and erlotinib. The percentage of *ras* mutations in NMSC widely varies: The values reported in clinical studies can range from 2 to 22% (24-26).

BCCs also express EGFR, but the key pathology in BCC is an aberration in the hedgehog (HH) pathway. HH is one of several pathways that orchestrate embryogenesis by exerting partial and temporal control over proliferation, survival and cell-fate decisions. In response to paracrine signals, HH can completely inhibit a protein termed Patched-1 (PTCH-1), provoking the removal of its inhibition upon Smoothened, an enzyme involved in cell proliferation. As a result, HH hyperactivation is able to stimulate Smoothened, activating a cell-proliferation pathway, which, in normal cells, is silent, although it becomes hyperactive during embryogenesis. Uncontrolled HH signalling is sufficient to promote tumorigenesis in basal skin cells. Major genetic changes causing BCC include inactivating mutations of PTCH-1 and activating mutations of Smoothened (27,28). Vismodegib is a small molecule that is able to inhibit Smoothened, and is commonly used in the treatment of advanced BCCs (29,30). A mounting body of evidence has demonstrated that, in a number of solid tumours, the ligand-dependent activation of HH signalling is potentiated through cross-talk with other critical molecular signalling pathways (31). Among these pathways are the Ras-RAF-mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinase (ERK) and the PI3K/Akt/mammalian target of rapamycin (mTOR) signalling pathways, and the EGFR and Notch signalling pathways. Thus, in NMSC, EGFR signalling acts synergistically with the HH pathway in the malignant transformation of cells (32).

On the basis of these findings, in the present review it is proposed that the hyperactivation of EGFR is a common feature in BCC and SCC, and that blockade of EGFR may be a therapeutic option for this category of tumours.

3. Locally advanced NMSC: The role of cetuximab

Standard options. Locally advanced NMSCs often are treated with Mohs surgery, and, when the risk of recurrence is high, with sentinel lymph-node dissection and, occasionally, with adjuvant radiotherapy or chemoradiation. Radiation or chemoradiation are employed only in patients not fit for surgery, due to disease extension, poor performance status or refusal of surgery. External beam radiation therapy for NMSC often consists of a three-dimensional conformal technique, using 6 MV energy photon beams, with the aim of striking the deep parts of the tumour and lymph nodes. An additional dose of radiation, using electrons, is often administered, with the aim of an improved coverage of the external component of the tumour. Usually, 66-70 Gy, in fractions of 2 Gy, are

administered (5). Radiation therapy technology has evolved with improved efficacy and, at the same time, a reduction in the dose of radiation to the surrounding normal tissue. Intensity-modulated radiation therapy provides an improved dose conformation and uniformity, with the sparing of normal tissues, and an improved target-volume coverage and lower toxicity. Concomitant chemoradiation has been demonstrated to markedly prolong patient survival rates compared with the survival rates with radiation alone; the drug most often used in clinical trials has been cisplatin (6). However, cisplatin, which is administered at a dose of 100 mg/m^2 of body surface for three weeks, is often associated with significant toxicity, in particular, nausea, vomiting and dysphagia. These toxic reactions frequently require discontinuation of the therapy, particularly in patients who are elderly (>75 years old) or who have a poor performance status. Owing to its toxicity, cisplatin may require substitution with a better-tolerated drug.

Cetuximab. Given the paucity of non-resectable or metastatic cutaneous SCCs, reliable information on the frequency of the tumours' EGFR expression is limited. However, in a clinical trial enrolling patients affected by SCC, Toll *et al* (33) demonstrated that the expression of EGFR, as determined by immunostaining experiments, markedly correlated with EGFR gene amplification, assessed by fluorescence *in situ* hybridization. Additionally, the expression of EGFR in SCC was markedly higher when compared with that observed in actinic keratotic and normal skin cells. Similarly, EGFR gene amplification was identified in a markedly higher proportion of SCC, with respect to actinic keratosis.

Cetuximab is a chimaeric human/murine monoclonal antibody, which binds competitively to EGFR and prevents activation of the receptor, thus blocking activation of its downstream pathways (34). Compared with currently approved chemotherapies for skin carcinomas, cetuximab is better tolerated, the most frequently encountered side effects being those concerning the skin, namely acneiform eruption, xerosis, paronychia, hair changes, telangiectasia and hyperpigmentation. In clinical trials, cetuximab has been shown to be fairly efficacious for recurrent or metastatic chemo-refractory NMSC. Kalapurakal *et al* (35) treated eight patients, whose disease progressed following first-line platinum-containing chemotherapy with single-agent cetuximab. Of the patients, five achieved a complete remission and three obtained a partial remission, with an overall response rate of 100%, although the duration of response was short: The disease in 63% of the patients progressed within six months.

The aforementioned study paved the way for further investigations of cetuximab in NMSC. Maubec *et al* (36) enrolled 36 patients with recurrent, metastatic inoperable BCC or SCC in a phase II trial. Cetuximab monotherapy was administered at a standard induction dose of 400 mg/m^2 of body surface, followed by a weekly dose of 250 mg/m^2 leading up to the progressive disease (PD) stage. A disease control rate (DCR), namely the sum of the complete response, partial response and stable disease at six weeks, was achieved in 25 patients (69%), with an overall response rate of 28%. Among the 31 evaluable patients, the development of an acneiform rash did not enable the prediction of a response to the treatment, although it did enable prediction of the mean progression-free survival and overall survival times. A number of case reports of cutaneous SCC patients treated with cetuximab also have been published, which have demonstrated that cetuximab may be a therapeutic option in patients with non-resectable cutaneous SCC (37,38).

Concurrent cetuximab radiotherapy. Treatment of patients with NMSC, particularly those who are unsuitable for surgery, with cetuximab and exclusive radiation therapy may be an intriguing strategy. Preneau *et al* (39) performed a phase II study of cetuximab for non-resectable SCC. Among 20 patients enrolled, five were selected for treatment with radiotherapy (60-70 Gy) with concurrent cetuximab, and the remaining patients were treated with carboplatin-cetuximab or cetuximab alone. After two months, the responses were evaluated, and as a result, no patient was identified who had a complete remission. Of the five patients, four (80%) had undergone a partial remission and the remaining patient (20%) registered with stable disease, with a DCR of 100%. The median progression-free survival was five months. Of the patients, four (80%) experienced a serious adverse event (grade 3-4); in particular, in-field skin toxicity, namely an acneiform rash in the irradiated area, was the most frequent side effect. Patients selected to receive radiotherapy plus cetuximab had a higher response rate compared with those who received carboplatin with cetuximab or cetuximab alone (80 vs. 44 vs. 33%, respectively).

Samstein *et al* (40) retrospectively analysed 12 patients treated with concurrent cetuximab-radiotherapy for locally advanced and non-resectable SCC. The patients were elderly: 75% had moderate to severe comorbidities, whereas 42% had immune dysfunction. Radiation therapy was delivered to all the patients via an intensity-modulated radiotherapy technique, reaching a median total dose of 60 Gy; cetuximab was administered according to the standard weekly schedule. Complete and partial responses were noted in 36 and 27% of the patients, respectively, with an overall response rate of 64% and a DCR of 91%. The median progression-free survival and overall survival times were 6.4 and 8.0 months, respectively. Considering the poor prognosis of the population, the response rate to this treatment was promising, although grade 2-3 adverse events were encountered in 83% of the patients: Skin rash was the most common, followed by fatigue, radiation dermatitis and infection. Almost 65% of the patients had side effects requiring hospitalization.

Helical tomotherapy represents a very important step in radiotherapeutic technical innovation, by allowing a further improvement in dose conformation and uniformity and the sparing of normal tissues. The association of helical tomotherapy and cetuximab has been documented in a case report (41). The patient was a 45-year-old woman, with a very advanced SCC arising from the sacral region and involving the spinal cord. A marked and durable response was observed on combining cetuximab with helical tomotherapy. Previously published data regarding this technique are few, although it is likely to deserve further investigation.

4. Conclusion

NMSCs are a very heterogeneous category of tumours, predominantly composed of BCCs, which originate from the

basal layer of the epidermis, and SCCs, which arise from keratinocytes in the superficial and corneous strata. BCCs have a low metastatic potential, although certain subtypes, particularly if poorly differentiated, may easily spread to the lymph nodes and distant sites. SCCs are more likely to be aggressive and invasive compared with BCCs, and the majority of locally advanced and advanced NMSCs are SCCs. Therapeutic strategies for locally advanced disease are similar for both diseases, and consist of surgery when possible, or surgery combined with chemoradiation. Little reliable information exists regarding the management of advanced NMSCs. Patients with advanced disease are relatively rare. Therefore, multi-institutional trials must be conducted to accrue adequate patient numbers. The literature primarily consists of isolated case reports and small case series. As discussed above, cisplatin-containing chemoradiotherapy is poorly manageable, and it may be substituted by cetuximab. At present, there is a lack of clinical trials assessing the efficacy of cetuximab in combination with radiation therapy in locally advanced NMSCs, and the majority of the trials are small, single-institution experiences, or case reports. One possible advance may be afforded by modification of the radiotherapy techniques, thereby allowing well-shaped irradiation, perfectly conformed on the target, and the coupling of radiotherapy with EGFR blockade. Nevertheless, skin toxicity observed in clinical trials has not been low.

Radiation dermatitis occurs in most patients receiving radiotherapy. Patients with SCC who receive radiotherapy in combination with EGFR inhibitors, including cetuximab, may develop a characteristic acne-like rash in addition to dermatitis. Radiation-induced keratinocyte damage induces DNA injury repair via activation of the p53 pathway and a simultaneous release of inflammatory cytokines as a consequence of the generation of free radicals, and, at the same time, keratinocytes demonstrate an increased expression of EGFR, possibly as a mechanism for repopulating irradiated areas (42). The use of EGFR inhibitors may be associated with the development of skin reactions, including a macular, papular, pustular rash, commonly referred to as acne-like rash, xerosis, fissures, telangiectasia and hair and nail changes (43). The pathophysiology of the skin reactions associated with EGFR inhibitors has yet to be fully elucidated, although the protein p27 may be involved, which is up-regulated on systemic cetuximab administration, leading to an impairment of the cell cycle, apoptosis and differentiation (44).

Several published clinical studies have been in favour of a multidisciplinary team management of these patients, with the joint aim of early recognition of any cutaneous side effects and administration of local and systemic drugs to resolve them (45). For example, the topical application of vitamin K3 (menadione), an EGFR phosphatase inhibitor, was shown to restore EGFR-mediated signalling in the skin, which had been altered by the administration of cetuximab (46).

Efficacy of the EGFR blockade has been observed for BCC and SCC: Gefitinib, a small molecule that inhibits EGFR, and panitumumab, a completely humanized monoclonal antibody directed against EGFR, have been demonstrated to have a certain amount of activity in NMSC (47,48). This last feature may depend on the biology of NMSC, since the EGFR pathway is often deregulated in SCC and in BCC. Notably, in BCC, crosstalk between the HH pathway, which represents the predominantly disrupted pathway in this category of tumours, and the EGFR pathway has been identified (30).

A future approach may be to associate an HH pathway inhibitor, such as vismodegib, with cetuximab in the treatment of BCC, or to employ EGFR inhibition earlier in SCC. The only problem that arises is the variable frequency of *ras* mutations in NMSC, which, in certain previous studies, has reached 22% (24-26).

In conclusion, the association of radiation therapy and cetuximab, as is possible in the case of concomitant HH targeting (for BCC), should be taken into account for the treatment of locally advanced NMSC in the future. Skin toxicity, which is associated with the concomitant administration of cetuximab and radiotherapy, may be best treated by recourse to multidisciplinary team management, which may lead to earlier detection and an improved resolution of cutaneous side effects.

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