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Melanoma and Cutaneous Malignancies

Treatment of Unresectable and Metastatic Cutaneous Squamous Cell Carcinoma

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ABSTRACT

Cutaneous squamous cell carcinoma (SCC) is an already common disorder with a rapidly increasing incidence. Treatment of early disease depends primarily on surgery or destructive techniques. In contrast to the frequency of early SCC, unresectable or metastatic SCC is relatively rare, but potentially life-threatening without clearly proven treatment options. Few rigorous studies of the treatment of advanced SCC have been undertaken. In the past, various agents have been explored in a limited fashion, including chemotherapy (cisplatin, fluoropyrimidines, bleomycin, doxorubicin), 13-cis-retinoic acid, and interferon-α2a. Clinical activity has been suggested by these trials, but their small sizes, heterogeneous patient populations, and lack of randomization have hindered the use of their results in defining treatment paradigms. Only one rigorous randomized trial has focused on cutaneous SCC. Enrolling 66 patients, that trial randomized patients at high recurrence risk to either observation or postoperative interferon-α2a and 13-cis-retinoic acid. This treatment did not improve time to recurrence or prevent secondary cutaneous SCC from developing. Though not in the metastatic setting, this study casts doubt on the ability of this regimen to control metastatic disease. Recently, agents targeting the human epidermal growth factor receptor (erlotinib, gefitinib, cetuximab) have displayed preliminary evidence of activity in phase II clinical trials and case series reports. Expression of this receptor is frequent in cutaneous SCC and appears to be prognostically adverse. Only the conduct of rigorous trials, with well-defined endpoints, adequate patient numbers, and preferably randomization, can prove the clinical efficacy of this promising treatment approach and define better therapy for this vexing clinical problem. ***The Oncologist*** 2010;15:1320–1328

INTRODUCTION

Nonmelanoma skin cancer (NMSC) is the most common malignancy worldwide, consisting primarily of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [1]. SCC, making up 20% of all NMSC cases, is the second most common skin cancer after BCC in the U.S. [2]. The lifetime risk for developing SCC is 7%–11%, and this has been increasing epidemically in the last several decades [3].

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SCC is generally more aggressive, and potentially life-threatening, than BCC. The mortality rate from SCC of the skin is difficult to estimate, partly because of inadequate data regarding its overall incidence. A study from Australia estimated the case fatality rate at 4%–5%, whereas U.S. studies suggest a 1% rate [4, 5]. Most (>90%) patients with SCC are cured by local therapies [6]. The remaining patients are not cured and require additional treatment.

Treatment of Early Disease

Primary SCC may be classified as low or high risk, depending on the likelihood of recurrence, metastasis, and death. Both tumoral and host factors may be important (Table 1) [7, 8]. The possession of any of the factors in Table 1 should alert the clinician to a less than optimal prognosis. For example, one prospective analysis of 210 cutaneous SCC patients identified primary tumor diameter ≥4 cm, invasion of s.c. tissues, and perineural invasion as adverse factors [5]. Patients possessing one of these high-risk factors displayed a 3-year disease-specific survival rate of only 70%, versus 100% for patients without any of these factors.

For low-risk, local lesions, the usual treatment is surgical excision, electrodessication, and curettage, or cryosurgery. Destructive treatment methods leave no tissue to analyze for marginal control. Nevertheless, using these methods, the 5-year control rate in patients with low-risk primary lesions can be as high as 96% [7, 9].

For higher risk tumors, the primary treatment is surgical excision. The key factor in determining the cure rate is the ability to achieve negative surgical margins [7, 8]. Surgery may be conventional or microscopically controlled, the later procedure referred to as "Mohs' surgery," after its originator. In this procedure, the targeted lesion is excised and the circumferential margins are assessed microscopically for residual tumor. Margins remaining involved undergo repeated excisions, followed by histological assessment, until negative margins are obtained. Mohs' surgery yields local control rates of 92%–100%, versus 38%–87% for standard surgical excision [10]. Mohs' surgery cure rates decrease as tumor grade increases, with a 45.2% cure rate for grade 4 SCC [9]. For inoperable, aggressive or recurrent lesions, adjuvant or primary radiation therapy may play a role [8, 10]. The extent of benefit conveyed by adjuvant radiation therapy has not, however, been clearly quantified.

Table 1. Factors increasing the risk for recurrence, metastasis, or death in patients with squamous cell carcinoma of the skin [7, 8]

Tumoral factors
Gross/clinical findings
Lesion diameter >1 cm
Location at embryonic fusion planes
Indistinct margins on clinical exam
Site of origin in burn, chronic wound, ulcer, or irradiated sites
Recurrent tumors
Location in anogenital region, ear, or lip
Histologic
Positive margins after resection of primary tumor
Poorly differentiated or infiltrating histology
Perineural/perivascular invasion
Basosquamous histology
Host factors
Coexisting chronic lymphocytic leukemia
Organ transplantation
Immunosuppressed host
Existence of any of these factors implies high risk.

Treatment of Advanced Disease

Cytotoxic Chemotherapy

In its most advanced form, cutaneous SCC is treated systemically. Investigation of systemic therapy for this disease has been very limited. Recommendations are based wholly on the results of one adjuvant phase III trial, four single-arm phase II trials, and a number of case series/reports. A number of systemic therapies have been used to treat advanced cutaneous SCC, including cytotoxic chemotherapy (cisplatin, 5-fluorouracil [5-FU], bleomycin, and doxorubicin), 13-cis-retinoic acid (13cRA), immunotherapy (interferon α2a [IFN-α]), and molecularly targeted agents (gefitinib, cetuximab, and erlotinib) (Table 2).

A nonrigorous randomized trial comparing bleomycin with other cytotoxic agents (cyclophosphamide, vincristine, methotrexate, and procarbazine) as treatment for 70 patients with SCC, only six of whom had cutaneous SCC, showed no statistically significant difference between the two treatment groups [11]. Sadek et al. [12] reported on 14 patients (13 evaluable) from a prospective observational study of patients with advanced cutaneous SCC treated with cisplatin, 5-FU, and bleomycin for 1–4 months. That study resulted in four of 13 patients with a complete response (CR) and seven of 13 with a partial response (PR) [13]. After 1 year, six of 13 patients had died from their disease and six of 13 had no evidence of disease. One patient who achieved a CR had local recurrence at 8 months, but achieved a second CR after surgery and adjuvant radiotherapy.

Two case series reported patients achieving a CR with

Table 2. Clinical trials, case series, and case reports of systemic therapy of advanced cutaneous squamous cell cancer

Trial design	*n*	Population	Treatments	Response rate	Survival	Comments	Reference
Phase III prospective randomized controlled study	66	Aggressive SCC, postsurgical adjuvant therapy	13-cRA daily and IFN-α 3× weekly for 6 mos versus no adjuvant therapy	Not applicable	Not reported	Treatment did not improve time to recurrence or prevent second primary tumors	21
Phase III prospective randomized study	70	Advanced SCC	Bleomycin 2× weekly up to 10 treatments versus physician's choice of chemotherapy	39% in both groups	Median survival about 200 days in both groups; not significantly different	Only 6 patients with cutaneous SCC; method of tumor assessment not described	11
Phase II prospective observational cohort study	32	Advanced inoperable SCC, pretreated	13-cRA daily and IFN-α daily	CR, 7 of 28; PR, 12 of 28; median response duration, 5 mos	One death related to disease progression (not included in results)	28 of 32 evaluable for response; association between lower response rate and greater extent of disease	6
Phase II prospective observational cohort study	39	12 with locally advanced SCC, 16 with regional metastasis, 11 with distant metastasis	13-cRA daily and IFN-α 3× weekly; cisplatin administered weekly	CR, 6 of 35; PR, 6 of 35	Median survival, 14.6 mos; no treatment-related deaths	35 of 39 patients evaluable	22
Phase II prospective observational cohort study	18	Advanced or recurrent SCC, pretreated	Gefitinib orally for 4 wks	SD, 4 of 15 after 4 wks	No deaths	Abstract; 15 patients evaluable for response	48
Phase II prospective observational cohort study	36	Advanced or metastatic SCC expressing EGFR, previously untreated	Cetuximab administered weekly	RR, 11%; CR, 1 of 36 (3%); PR, 8 of 36 (22%); SD, 15 of 36 (42%); DCR, 69% at 6 wks	Mean PFS, 121 days; mean OS, 246 days; 6 deaths related to disease progression; 7 deaths total, judged not related to cetuximab	Abstract; primary endpoint, DCR at 6 wks; possible association of rash and PFS/OS	40
Prospective observational study	14	Aggressive and recurrent SCC, pretreated	Oral 5-FU for 3 wks every 5 wks	PR, 2 of 14; SD, 4 of 14	Median duration of response in those with PR or SD, 30 wks		20
Prospective observational study	14	Advanced SCC, pretreated	Cisplatin, 5-FU, and bleomycin	CR, 4 of 13; PR, 7 of 13	6 of 13 dead from disease; 6 of 13 no evidence of disease	13 patients evaluable	12
Prospective observational study	12	Advanced SCC, combination of untreated and pretreated	Cisplatin and doxorubicin; chemotherapy alone ($n = 7$), or neoadjuvant to surgery ($n = 1$) or radiation ($n = 4$)	CR, 4 of 12 (33%); PR, 3 of 12 (25%)	5 of 12 with progressive disease, including one death; 4 of 12 alive with no evidence of disease at time of report	Two with no evidence of disease were patients who achieved a CR with chemotherapy alone; 28 patients were enrolled in the trial, but only 12 with cutaneous SCC	17
Case report	7	Advanced locoregional or metastatic SCC, untreated	Cisplatin and 5-FU	CR, 3 of 7; PR, 3 of 7	1 of 7 died from disease progression		14
Case report	4	Advanced SCC, untreated	Capecitabine and IFN-α 3× weekly	CR, 2 of 4; PR, 2 of 4	1 patient died from unknown causes		19
Case report	3	Refractory SCC, pretreated	Cisplatin and doxorubicin	CR, 1; PR, 1	2 of 3 died from disease		16
Case report	2	In-transit recurrence; moderate to poorly differentiated SCC, pretreated	Cetuximab weekly over 3–6 mos	CR, 1; PR, 1			44
Case report	2	Patient 1, SCC on the face and recurrent submental mass; patient 2, SCC of the temple; both pretreated	Erlotinib for 1–3 mos	Patient 1, CR after 1 mo; patient 2, PR after 3 mos		Patient 1, mass recurred upon stopping erlotinib; CR again achieved upon erlotinib readministration	50
Case report	2	Locally advanced SCC	Cisplatin and 5-FU	Patient 1, CR after 3 mos; patient 2, CR after first course of therapy	Patient 1, died from other causes; patient 2, died from disseminated disease	Abstract	15
Case report	2	Aggressive SCC on the face, pretreated	Patient 1, cisplatin and doxorubicin for 2 cycles followed by carboplatin and doxorubicin for 3 cycles; patient 2, mitoxantrone and carboplatin for 1 cycle	Patient 1, CR for 8 mos; patient 2, CR after electron beam irradiation	Patient 2, died from cardiac arrest 2 mos after interrupting treatment	Mitroxantrone and carboplatin used in patient 2 because of borderline-low cardiac ejection fraction	18
Case report	1	Unresectable poorly differentiated SCC, pretreated	Cetuximab	Response after 7th wk of treatment; relapse after discontinuing; CR after 7 more weekly infusions	After 2 mos of weekly treatments following CR, became refractory to cetuximab and disease progression led to death		45

Abbreviations: 5-FU, 5-fluorouracil; 13-cRA, 13-cis-retinoic acid; CR, complete response; DCR, disease control rate; IFN-α, interferon-α2a; OS, overall survival; PFS, progression-free survival; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease.

the combination of cisplatin and 5-FU [14, 15]. Khansur et al. [14] reported on seven patients with primary cutaneous SCC and locoregional progression treated with cisplatin and 5-FU. A CR was achieved in three of seven patients and

a PR was achieved in three of seven patients. The median duration of CR was 1 year. Two of the three patients with a CR were disease free at a 13-month and 24-month follow-up. Fujisawa et al. [15] reported on two patients achieving a CR after one or two cycles of cisplatin and 5-FU. In one of the patients, therapy was discontinued after achieving a surgically confirmed CR. That patient eventually developed disseminated disease, leading to death 2 years after initial presentation. The authors concluded that this therapy appeared to be effective in terms of local control, but was ineffective in preventing hematologic dissemination.

Guthrie et al. [16] treated three SCC patients with cisplatin and doxorubicin. One patient had a CR for 17 months, one had a PR for 3 months, and one had stable disease (SD). The authors suggested that the combination of cisplatin and doxorubicin had activity in cutaneous SCC. A phase II trial by the same group used this regimen in 12 cutaneous SCC patients [17]. Interpretation of that trial's results was hampered by the low numbers of enrolled patients and their heterogeneity. Seven patients were treated with chemotherapy alone: two achieved a CR for 4–12 months, two achieved a PR for 3–6 months, and three had no response. Five patients received neoadjuvant chemotherapy followed by surgery ($n = 1$) or definitive radiation therapy ($n = 2$), with two CRs and one PR after induction chemotherapy. The authors concluded that this combination had activity in advanced cutaneous SCC patients, and that multimodality therapy was to be preferred over chemotherapy alone. A case report of combined cisplatin and doxorubicin-based therapy also indicated that this combination may be active [18].

Wollina et al. [19] used oral capecitabine and s.c. IFN-α in four patients with advanced cutaneous SCC. Capecitabine is an orally bioavailable fluoropyrimidine chemotherapy agent that is converted to 5-FU in tumor cells. They reported two patients with CRs and two patients with PRs using this regimen.

Oral 5-FU was administered to 14 patients with advanced cutaneous SCC as a single agent [20]. Two patients experienced a PR and seven had SD of varying duration. This 5-FU preparation is not commonly available in the U.S. This report, however, supports the use of fluoropyrimidine-based therapy in advanced cutaneous SCC patients, because there may be palliative benefit even with the use of single-agent therapy.

Retinoids and IFN-α in Cutaneous SCC

Retinoids modulate cell differentiation and proliferation; in vitro, some cytokines can act synergistically with retinoids to inhibit cell proliferation and increase apoptosis [21]. Shin et al. [22] assessed the effects of IFN-α, 13cRA, and cisplatin used to treat unresectable SCC of the skin in a prospective phase II trial. Thirty-nine patients were enrolled and 35 were considered evaluable. Of these, six of 35 (17%) experienced a CR and six of 35 (17%) had a PR. The response rate of patients with locoregional disease was higher (67%) than that of patients with metastatic disease (17%; $p = .007$). They concluded that this combination was useful in treating locally advanced disease, but less so in metastatic disease.

Lippman et al. [6] used 13cRA in combination with IFN-α in a prospective phase II trial enrolling 32 patients with inoperable cutaneous SCC. They observed a response in 19 (68%) of the 28 evaluable patients (seven CRs, 12 PRs). The median duration of response was 5 months. Response rates varied with the extent of disease: 93% (13 of 14) responded among patients with advanced local disease, 67% (four of six) responded among patients with regional disease, and 25% (two of eight) responded among those with distant metastases. This combination appeared to be effective in advanced SCC patients, albeit with greater efficacy in less advanced disease.

Although not focused on treatment of unresectable disease, Brewster and coworkers reported on a phase III trial testing whether adjuvant therapy with 13cRA and IFN-α was effective in preventing recurrences and increasing time to recurrence [21]. Their adjuvant study enrolled 66 patients with "aggressive" SCC, defined as having one of the following characteristics: size $\geq$2 cm, perineural invasion, radiological or pathological evidence of deep invasion into nearby structures, or proven regional metastasis. The 66 patients were randomly assigned, following initial surgery, to receive either a combination of 13cRA and IFN-α for 6 months or no systemic adjuvant therapy. Adjuvant radiotherapy was added to the initial treatment plan for tumors with perineural invasion, more than two positive nodes, extracapsular nodal disease, or microscopically positive margins. With a median follow-up of 21.5 months, this systemic treatment did not improve time to recurrence or prevent secondary tumors. Although this study was in the adjuvant setting, the results argue that this combination is unlikely to be highly active in the setting of macroscopic residual disease. This is particularly notable given the relatively high quality of this study, compared with others testing this regimen or indeed any other regimen in this disease.

The Human Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR, HER-1, erbB) is a transmembrane receptor tyrosine kinase that belongs to a family of four kinases, with the other members being designated HER-2, HER-3, and HER-4 [23, 24]. Binding of any of several ligands to the extracellular do-

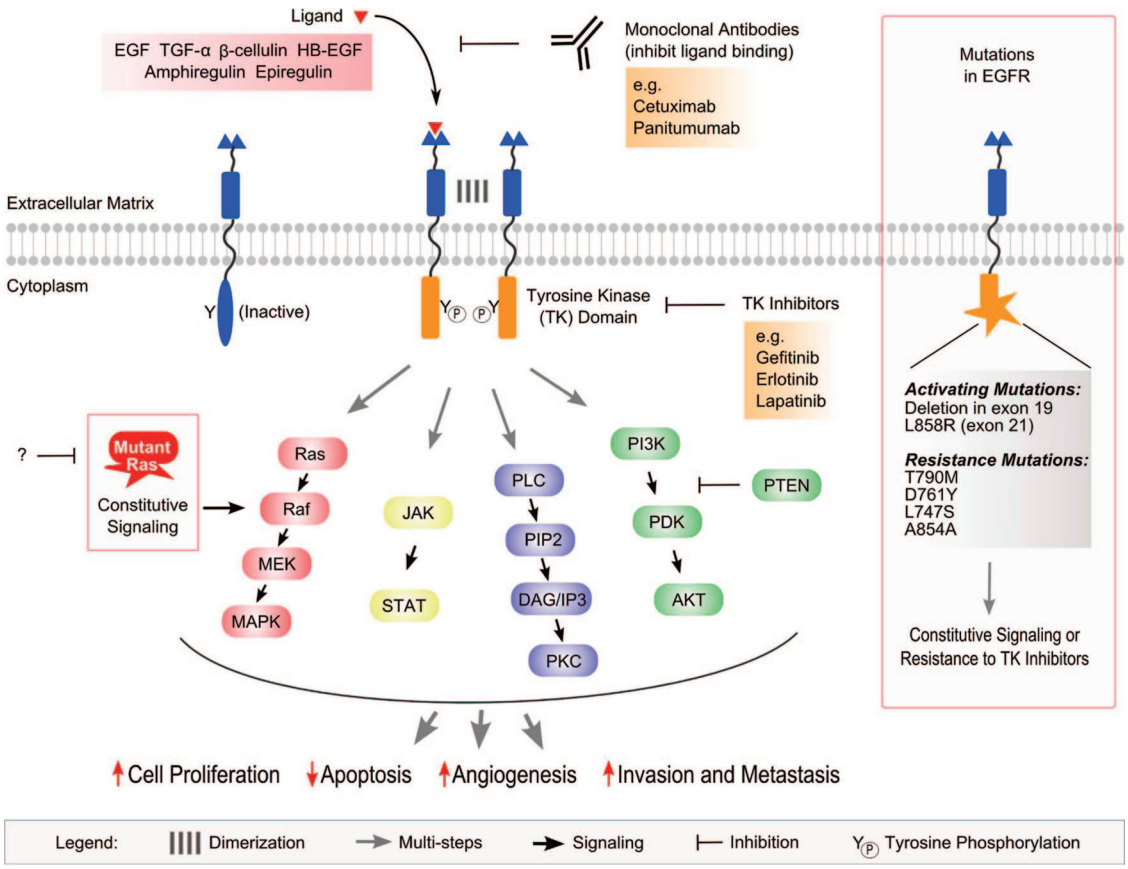

Figure 1. Signaling pathways and effects of EGFR. Upon binding to one of multiple ligands, EGFR dimerizes with another member of the EGFR family, leading to the activation of the TK domain, phosphorylation of critical tyrosine residues in the EGFR intracellular domain, and activation of downstream signaling pathways, including MAPK, JAK-STAT, PLC, and PI3K–Akt. Collectively, EGFR signaling may lead to increased cell proliferation, decreased apoptosis, increased angiogenesis, increased invasion, and increased metastasis. As depicted above, multiple opportunities exist to inhibit EGFR signaling; for example, monoclonal antibodies (e.g., cetuximab and panitumumab) interact with the extracellular domain of EGFR preventing ligand-induced activation of the receptor, and small-molecule inhibitors (e.g., gefitinib, erlotinib, and lapatinib) block activation of the TK domain preventing induction of EGFR signaling pathways. Specific *EGFR* mutations may lead to constitutive activation of EGFR regardless of ligand binding and/or resistance of EGFR to the effects of TK inhibitors. Independent of receptor status, EGFR downstream signaling may become aberrantly activated; for example, mutant *Ras* may lead to constitutive activation of the MAPK pathway or mutation/loss of *PTEN* may lead to loss of negative regulation of the PI3K–Akt pathway.

Abbreviations: DAG, diacylglycerol; EGFR, epidermal growth factor receptor; IP3, inositol triphosphate; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK, MAPK/extracellular signal–related kinase kinase; PDK, 3-phosphoinositide-dependent protein kinase; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol bisphosphate; PKC, protein kinase C; PLC, phospholipase C; PTEN, phosphatase and tensin homologue deleted on chromosome ten; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TK, tyrosine kinase.

main of the receptor results in formation of EGFR homodimers and heterodimers with other members of the family. The intracellular domain of the receptors is activated in the dimerization process, leading to autophosphorylation of tyrosine residues and to phosphorylation and activation of downstream pathways (Fig. 1). These include Ras/Raf/mitogen-activated protein kinase (MAPK), phospholipase C, phosphatidylinositol 3-kinase (PI3K)–Akt, and Janus kinase–signal transducer and activator of transcription (JAK-STAT) [25]. The MAPK pathway is involved in cell proliferation and survival. The PI3K–Akt pathway is involved in cell proliferation and cell migration. The JAK-STAT pathway is involved in the transcription of genes involved in oncogenesis. The different EGFR signaling pathways are depicted in Figure 1.

The EGFR pathway is important in a range of cancers. Positive randomized trial results have led to the approval of agents targeting these pathways in non-small cell lung cancer, colorectal cancer, squamous cell cancer of the head and neck, and pancreatic cancer [26–30]. The relationship between this therapy and benefit is not, however, simple. Different factors predict response in different types of tumors.

A variety of biomarkers have been analyzed to assess their utility in predicting benefit. For example, in metastatic colorectal cancer treated with cetuximab, a monoclonal antibody targeting the extracellular domain of EGFR, the presence of activating mutations in exon 2 of downstream *KRAS* either leads to no benefit of cetuximab monotherapy or confers an adverse effect on outcome when cetuximab is combined with chemotherapy and bevacizumab [27, 31]. In contrast, *KRAS* exon 2 mutational status did not correlate with benefit in a study of non-small cell lung cancer patients treated with cetuximab and chemotherapy [32]. The presence of activating mutations in *EGFR* itself, elevated *EGFR* gene copy number, and positive immunohistochemistry (IHC) for EGFR have been shown, in randomized trials, to be useful in predicting benefit from small molecule inhibitors directed at the EGFR tyrosine kinase domain [33–35].

Given the paucity of unresectable or metastatic cutaneous SCC, reliable information on the frequency of EGFR expression is limited. One study of 13 metastatic specimens by IHC demonstrated that all had strong membranous expression of EGFR [36]. Another study of locally advanced and nodally metastatic cutaneous SCC demonstrated EGFR expression above background in only nine of 21 (43%) specimens using a quantitative Western blotting technique [37]. Another study using IHC and fluorescence in situ hybridization demonstrated higher levels of EGFR protein expression in cutaneous SCC than in the precursor actinic keratoses and an association between this elevated protein expression and higher *EGFR* gene copy number [38]. One study, examining the role of EGFR in cutaneous SCC arising in the head and neck, demonstrated that primary lesions associated with subsequent metastasis were more likely to overexpress EGFR (79%) than those not associated with subsequent metastasis (36%) [39]. Interestingly, metastatic nodal disease exhibited only a 47% rate of EGFR overexpression; EGFR overexpression in that study was not associated with *EGFR* gene amplification.

Anti-EGFR Therapy in Cutaneous SCC

Cetuximab, a humanized monoclonal antibody, inhibits EGFR by blocking the extracellular domain of EGFR. This prevents the receptor's ligand from binding and consequent dimerization. One phase II study and two case reports have described its effects in cutaneous SCC. Maubec and coworkers recently reported final results from a phase II trial enrolling 36 patients with unresectable or metastatic cutaneous SCC that expressed EGFR [40]. None of the patients received prior chemotherapy. Thirty-one patients of 36 enrolled were evaluable for tumor response. The study's primary endpoint was the disease control rate (DCR = CR + PR + SD) after 6 weeks of treatment. In the intent-to-treat population, the DCR was 69% and the overall response rate was 11%. The mean progression-free survival (PFS) and overall survival (OS) times were 121 days and 246 days, respectively. Grade 3–4 toxicities judged to be associated with cetuximab therapy were seen in three patients (infusion-related reactions in two patients and interstitial pulmonary syndrome in one patient). Among the 31 evaluable patients, development of an acneiform rash did not predict response to treatment, but did predict the mean PFS and OS times. Such drug rashes have been associated with better outcome in other diseases treated with cetuximab, such as SCC of the head and neck [28].

Randomized trials of cetuximab in metastatic colorectal cancer (mCRC) patients have confirmed the importance of mutational status in the signal transduction apparatus downstream from EGFR, including *KRAS* and *BRAF*, and in an immune marker, the Fc antibody receptor [41–43]. In a subset of 28 patients studied by Maubec and coworkers, mutational status was assessed in exon 2 ($n = 28$) and exon 3 ($n = 25$) of *KRAS* and exon 15 ($n = 23$) of BRAF kinase. All were found to be wild-type; mutations in these sites in mCRC patients predict lower responsiveness to cetuximab. Cutaneous SCC patients possessing the FcγIIa-131 H/H or FcγIIIa-158 V/V variants, associated with better outcome in mCRC patients, had a PFS interval similar to the wild-type 131R and 158F carriers in the Maubec et al. [40] study.

Two case reports of cutaneous SCC patients treated with cetuximab have also been published, both achieving CRs [44, 45]. All three reports suggest that cetuximab may be a therapeutic option in patients with unresectable cutaneous SCC. These results must be taken with caution, because they are preliminary. One report of two lung transplant patients receiving cetuximab for advanced cutaneous SCC suggested that fatal diffuse alveolar damage may have been caused by cetuximab [46]. Four cases of interstitial pneumonitis and one fatality are reported in the cetuximab package insert, of 1,570 patients treated [47].

Gefitinib inhibits binding to the ATP-binding site of EGFR, rendering it unable to autophosphorylate and activate the receptor. Glisson et al. [48] used gefitinib in a prospective phase II trial, enrolling 18 patients with advanced or recurrent cutaneous SCC. Gefitinib had already been reported to have an 11% response rate and 53% control rate in head and neck SCC patients [49]. Four of the fifteen evaluable cutaneous SCC patients had SD after 4 weeks of treatment.

Erlotinib, much like gefitinib, competitively binds to the ATP-binding site of EGFR. It has been approved for use in non-small cell lung cancer patients who have failed to respond to chemotherapy, and in advanced pancreatic cancer patients, combined with gemcitabine. Read et al. [50] reported results from two patients with unresectable cutane-

Table 3. Prospectively evaluated systemic therapy regimens for advanced cutaneous squamous cell carcinoma

Regimen	Comments	Reference
Bleomycin, 30 mg i.m. twice weekly	Maximum dose, 300 mg; likely obsolete regimen	11
5-FU oral administration; first cycle daily dose: 100 mg/m^2 on days 1–3, 150 mg/m^2 on days 4–7, 175 mg/m^2 on days 8–21; second and subsequent cycles (if tolerated): 175 mg/m^2 daily on days 1–21	Tablets for oral administration not available in the U.S.; low and inconsistent oral bioavailability; repeat dosing every 5 wks	20
Cisplatin, 100 mg/m^2 i.v. on day 1; 5-FU, 650 mg/m^2 continuous i.v. on days 1–5 or 1 g/m^2 on days 1–3; bleomycin, bolus 16 mg i.v. on day 1; bleomycin, continuous i.v. 16 mg/m^2 per day on days 1–5 or 25 mg/m^2 per day on days 1–3	Treatment repeated every 21–28 days; alternate dosing regimens for 5-FU and bleomycin yield approximately the same overall dose per cycle	12
Cisplatin, 75 mg/m^2 i.v. on day 1; doxorubicin, 50 mg/m^2 i.v. on day 1	Repeated every 21 days	17
IFN-α, 3 million units s.c. daily; 13cRA, orally 1 mg/kg daily	Treatment is given for: at least 2 mos unless obvious progression or tolerance; 3 mos if stable; 4 wks past CR; or indefinitely in PR if tolerated until either CR (then 4 more wks) or progression	6
IFN-α, 5 million units/m^2 s.c. three times weekly; 13cRA, orally 1 mg/kg daily; cisplatin, 20 mg/m^2 weekly		22
Gefitinib, 250 mg PO daily	Restricted availability for use in the U.S. (as of August 2010)	48
Cetuximab, 400 mg/m^2 i.v. wk 1, followed by 250 mg/m^2 i.v. weekly thereafter		40

Abbreviations: 5-FU, 5-fluorouracil; 13-cRA, 13-cis-retinoic acid; CR, complete response; IFN-α, interferon-α2a; PO, orally administered; PR, partial response.

ous SCC. One patient achieved a CR after 1 month of treatment and the other achieved a PR after 3 months of treatment. The patient that achieved a CR had a recurrence when the therapy was discontinued.

Treatment Recommendations

Treatment recommendations in this setting are difficult to promulgate, because the quality of information available is clearly suboptimal. If available, a clinical trial should be the first choice for treatment of these patients. Such trials are uncommon, because of the relative rarity of the condition. Furthermore, patients requiring treatment for advanced SCC may have serious medical comorbidities (such as iatrogenic immunosuppression for organ transplant) that prevent clinical trial participation, even if disease-specific trials are available.

Table 3 provides details of the systemic treatment regimens that have been studied prospectively and are described herein. Several of these regimens appear to be obsolete (i.m. bleomycin) or use a preparation (oral 5-FU) that may not be easily obtainable [11, 20]. Beyond this, no specific efficacy data argue for the use of any particular regimen in the off-protocol treatment of cutaneous SCC. All the prospectively studied regimens demonstrate clinical benefits in some patients, albeit in small studies with significant design limitations. Thus, logistical considerations and patient comorbidities play a major role in treatment selection. Platinum- or fluoropyrimidine-based systemic chemotherapy regimens could be considered standard cytotoxic regimens. Combinations of 13cRA and IFN-α would also be reasonable systemic options.

Despite the limited information regarding the use of EGFR inhibitors in cutaneous SCC, the volume of evidence for efficacy, in reported numbers of treated patients, approximates that supporting any other treatment regimen, and this is likely to continue to accumulate. EGFR inhibitors may also be tolerable in clinical situations in which cytotoxic or biological therapies may be contraindicated. Furthermore, phase I clinical trials of EGFR-targeting agents are likely to be available as new agents are developed, offering a possible avenue for biologically rational

treatment of these patients in an experimental setting, without requiring a disease-specific trial.

If a patient is not eligible for a clinical trial, but requires palliative therapy for advanced cutaneous SCC, treatment with an EGFR-inhibiting agent might be appropriate. The largest trial of EGFR inhibition completed to date assessed cetuximab. Data also exist for gefitinib. The choice of agent may, however, be dictated by nonmedical considerations, such as which EGFR-inhibiting agent can be obtained for a given patient. Assessment of tumoral EGFR expression, easily performed by IHC in most pathology laboratories, would be reasonable to confirm that the biological target of EGFR-inhibiting agents is at least present prior to treatment. Notably in this regard, the study of Maubec and coworkers required EGFR expression for participation [36, 40].

Conclusions

Although cutaneous SCC is quite common, surprisingly little reliable information exists regarding the management of advanced disease. The literature primarily consists of isolated case reports and small case series. Several prospective studies have been conducted, but they are hampered by limited study designs, relatively small patient numbers, and the consequent requirement for enrolling a heterogeneous group of patients. Studies using 13cRA and IFN-α, with or without cisplatin, seem to be the most rigorous, and suggest clinical activity in the metastatic setting. Enthusiasm for the nonexperimental use of these regimens must be tempered by the negative results of the only rigorous randomized trial in this disease setting, in which adjuvant therapy with 13cRA and IFN-α was ineffective [21]. Rigorous studies of chemotherapy in this disease have demonstrated activity, but have only been conducted in the phase II setting, and are similarly afflicted by limited patient numbers.

Targeting EGFR may be a biologically rational approach to the treatment of cutaneous SCC. EGFR is expressed in a significant fraction of cutaneous SCC tumors. Approved agents targeting this receptor exist, and data from phase II trials of gefitinib and cetuximab suggest clinically significant activity. Further rigorous trials are warranted. Strong correlative studies would be highly desirable; the extensive investigation of the EGFR pathway in other tumors should provide more than adequate guidance to the investigative plan in these efforts.

Significant barriers exist to the rigorous assessment of strategies to treat advanced cutaneous SCC. Patients with advanced disease are relatively rare. Thus, multi-institutional trials must be conducted to accrue adequate patient numbers. Reliable baseline data regarding the efficacy of existing treatment regimens (such as carboplatin and paclitaxel, widely used in other types of SCC but without data in cutaneous SCC) must be generated, both to assess activity and for comparison in future studies of novel agents, such as EGFR inhibitors. Finally, positive findings must be confirmed in well-conducted randomized trials, accompanied by correlative studies to validate (or exclude) potential biomarkers of activity. Only by doing so can new treatment paradigms for this vexing problem come to fruition.

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