Drug therapy of advanced cutaneous squamous cell carcinoma: is there any evidence?

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Purpose of review
There are few randomized controlled studies to guide the treatment of advanced cutaneous squamous cell carcinoma. The existing treatments are mostly based on case reports and small case series. Here we review recently available insights concerning the treatment of locally advanced and metastatic squamous cell carcinoma, with a special emphasis on novel targeted therapy and immunotherapy.

Recent findings
Surgery and combination of chemotherapy and radiation therapy have been long considered the gold standard options for advanced squamous cell carcinoma. The detection of clinically relevant driver mutations has opened the door to the use of novel targeted therapies. Recent studies have shown that aggressive cutaneous squamous cell carcinoma is characterized by a very high mutational background. Furthermore, the importance of the defective immunosurveillance in the growth of cutaneous squamous cell carcinoma and the critical role of programed cell death protein 1 and programmed death-ligand 1 interaction in skin tumor development provides a rationale for the use of immune checkpoint inhibitors.

Summary
Epidermal growth factor receptor inhibitors have shown to have satisfactory antitumor activity with acceptable side-effect profile. However, their place in management of advanced cutaneous squamous cell carcinoma alone or in combination with either radiation therapy and/or chemotherapy needs to be better characterized. The available preliminary findings suggest that immune checkpoint inhibitors represent a potentially valuable alternative in cutaneous aggressive squamous cell carcinoma, promising a further expansion of their indication spectrum. Randomized controlled studies will allow us to better characterize their practical value.

Keywords
antiepidermal growth factor receptor, cutaneous squamous cell carcinoma, immune checkpoint inhibitors, immunotherapy, metastasis

INTRODUCTION

Cutaneous squamous cell carcinomas (cSCC) represent the second most-frequent skin cancer [1]. cSCC are associated with significant morbidity and are responsible for the majority of nonmelanoma skin cancer (NMSC) deaths. Several risk factors for recurrence and metastasis have been identified, such as large tumor diameter, poor histological differentiation and immunosuppression [2].

Definitive management of early or small cSCC primarily relies on local therapies including topical agents, thermal ablation, surgical resection or radiation. However, in cases of locally advanced inoperable disease and metastatic disease, palliative radiotherapy and/or classical chemotherapies can offer modest clinical benefit. There is a critical need for improved treatments in advanced cSCC patients.

Two general approaches that have made substantial improvements in systemic agents in oncology have been the use of molecular targeted agents and immune modulation. Epidermal growth factor receptor (EGFR) and its family members are often

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Curr Opin Oncol 2017, 29:129–135

DOI:10.1097/CCO.0000000000000359

KEY POINTS

- The gold standard options for locally advanced inoperable cutaneous squamous cell carcinoma have been chemotherapy and/or radiation therapy, but the overall responses are often poor and unsatisfactory.
- EGFR inhibitors have been increasingly used for advanced cutaneous squamous cell carcinoma and have shown antitumor activity.
- There is a strong biological rationale for the use of immune checkpoint inhibitors, such as anti-PD-1 antibodies in advanced squamous cell carcinoma. The preliminary results are encouraging but need to be confirmed in controlled studies.

overexpressed or activated in human carcinomas including cSCC and may contribute to enhance uncontrolled proliferation. Anti-EGFR therapies have clinical benefit alone or in combination with chemotherapy and radiotherapy. The rat sarcoma viral oncogene homolog–mitogen-activated protein kinases signaling pathway, which is involved in regulating growth and proliferation of cSCC, represents another new potential therapeutic target.

Current immune modulation strategies attempt to generate a new antitumor response or to allow a natural immune response to control tumor growth. The development of cSCC is critically affected by a defective immune surveillance with lack of tumor-reactive T cells suggesting a role for immune control of these tumors [3]. Recent studies have indicated that cSCC is highly mutated, displaying a complex genetic background [4▪▪]. Blocking either CTLA-4 or programed cell death protein 1/programmed death-ligand 1 (PD-1/PD-L1) on T cells generates antitumor responses taking advantage of tumor mutations or 'neoantigens'. Finally, certain types of cSCC express PD-L1 and transgenic mice overexpressing PD-L1 in the epidermis exhibit accelerated development of cSCC [5]. In this context, immune checkpoint antibodies that block the PD-1/PD-L1 pathway and thereby increase the T-cell-specific immune response represent a novel promising therapeutic approach, which has been anecdotally used with encouraging preliminary results.

EPIDEMIOLOGY

Since the 1960s, the worldwide incidence of NMSC has been constantly increasing. Fair-skin individuals living in countries close to the equator and tropics are the most commonly affected patients. In fact, exposure to ultraviolet (UV) radiation and sunlight represent the greatest risk factors for the development of cSCC with a clear mutational signature of UV radiation [6]. Australia has the highest incidence in the world, with over 300 000 patients diagnosed per year. One study has estimated a diagnosis rate of 15–35 cSCC per 100 000 people, with an average increase of 2–4% per year [7]. In the United States, up to 420 000 new cases of cSCC have been estimated to occur in 2012 [8]. Although only 5% will become locally advanced, recur or metastasize, this still represents a significant problem (Figs 1 and 2). Their overall fatality rate is estimated between 1 and 5%. A large study reviewing 603 patients with metastatic cSCC found that 89% of patients with distant metastasis died of their disease at 5 years [9,10].

AVAILABLE TREATMENTS: OVERVIEW

Therapeutic options for cSCC include surgery, radiotherapy, chemotherapy, electrochemotherapy [11], targeted pharmacologic therapy and/or immunotherapy. Treatment of cSCC depends on the involvement of regional lymph nodes, distant metastasis and/or inoperable metastatic disease [12]. However, there is currently no clear standard of care for locally advanced unresectable and metastatic cSCC. Furthermore, the general condition of the patient, patient's age, associated comorbidities and immunosuppression state are important variables that should be considered for appropriate management [13].

Current management of regional spread (draining lymph node basin) is surgical excision with consideration of adjuvant radiation [14,15▪▪]. Surgery may be performed in patients with metastasis when tumor characteristics (i.e. size, location and number) allow for complete removal at or near the primary tumor site [15▪▪]. However, improved local disease control may be achieved when radiotherapy is used in combination with surgery. Veness *et al.* [16] assessed the results obtained in 167 patients over a 20-year period. Their findings indicate that patients undergoing combined treatment had a lower rate of locoregional recurrence as well as a significantly better 5-year disease-free survival rate compared with surgery alone [16]. Hence, radiotherapy should be discussed as an adjuvant therapy [17], especially in the case of locally advanced cSCC with high recurrence risk or metastatic cSCC. However, in certain settings, it can also be employed as a monotherapy [15▪▪].

CHEMOTHERAPY AGENTS

Platin derivates, that is, cisplatin or carboplatin, have been commonly used as the first-line

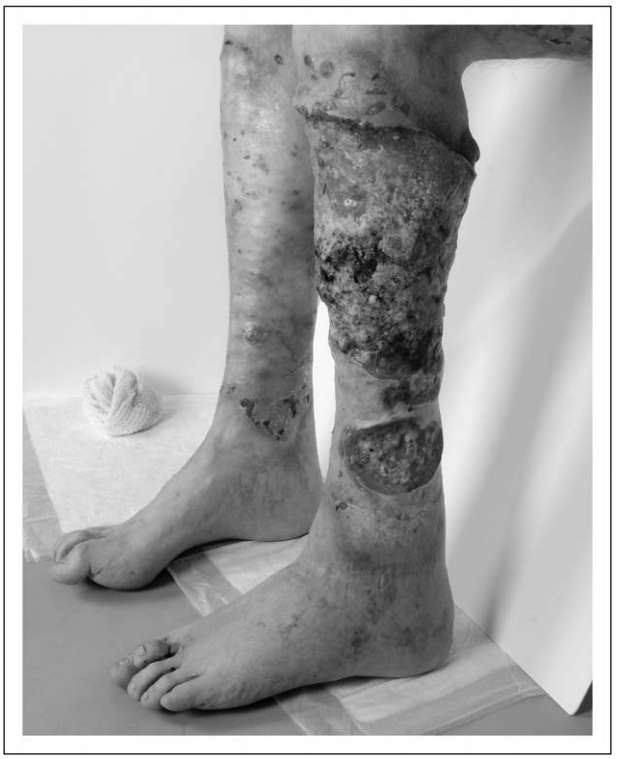

FIGURE 1. Advanced cutaneous squamous cell carcinoma developing on the left leg. Large ulcerated, partially necrotic, local invasive and destructive lesions.

molecules for advanced unresectable or metastatic cSCC but with limited clinical trial experience [18]. A recent single-center report suggested that patients treated with cisplatin benefited with improved response rates (RRs) and survival compared with patients receiving other systemic agents. The study was limited in size and was not randomized [19▪]. Other molecules used for either advanced or metastatic disease include 5-fluorouracil (5-FU), bleomycin, methotrexate, adriamycin, taxanes, gemcitabine or ifosfamide alone or in combination [15▪▪]. RRs with single agents vary widely from 17 to 78% [20,21]. Platins and 5-FU are often used as palliative treatment alone or in combination with radiotherapy [22]. Polychemotherapies seem more effective than monochemotherapy but result in more side effects and poor tolerance. There is currently no standard treatment of metastatic disease. Combinations of cisplatin with either 5-FU, doxorubicin or bleomycin have demonstrated some degree of efficacy, achieving complete responses in some cases [23]. The current National Comprehensive Cancer Network guideline suggests cisplatin either alone or in conjunction with 5-FU as first line, but underlines the fact that available data are weak and inconsistent and that newer options should be considered [24].

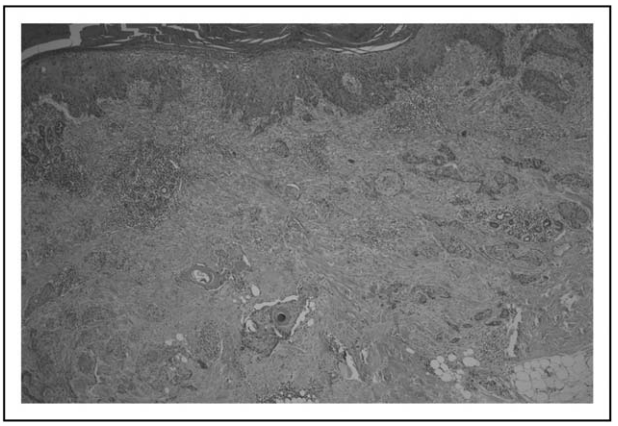

FIGURE 2. Light microscopy studies of a biopsy specimen obtained from an infiltrative growing cutaneous squamous cell carcinoma. Atypical acanthotic epidermis with hyperkeratosis and parakeratosis. Diffuse dermal infiltration of the tumor originating in the epidermis with strands and clusters of cells, focal horn pearl formation and dyskeratotic cells. Several atypical keratinocytes with large eosinophilic cytoplasm, mitoses and marked pleomorphism.

NOVEL TARGETED THERAPY: EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Advanced patient's age, poor general condition or medical comorbidities may preclude the use of conventional chemotherapy [25,26]. In this context, the identification of targetable driver mutations important for cSCC progression opens the door to new *targeted* therapies [27]. Previous studies have shown that up to 80% of cSCC and 100% of metastatic cSCC express EGFR [28]. The predictive role of EGFR mutations and EGFR signaling in cSCC is still debated [29,30]. The presence of activating mutations in *EGFR* itself, elevated *EGFR* gene copy number and/or aberrant expression of EGFR in tumor cells have been shown to constitute predictive markers of response to EGFR inhibition in clinical trials [31]. Both antibody-based inhibitors of the extracellular domain of EGFR and small molecule inhibitors of intrinsic tyrosine kinase activity are available for targeted therapies.

Two monoclonal EGFR targeting antibiodies have been evaluated in cSCC, cetuximab and panitumumab. Cetuximab is a chimeric monoclonal IgG1 antibody that prevents ligand-induced activation of EGFR and mediates a variety of antitumor activities [32]. So far, the most important study in cSCC is a phase II trial of Maubec *et al.* [33], in which cetuximab was used as first-line treatment in 36 patients. Disease control could be achieved in 69% of the intention-to-treat population at week 6. Two complete remissions and eight partial remissions

were observed with acceptable skin toxicity. The paucity of controlled trials and the low number of patients described in retrospective case series and single case reports limit the conclusions.

Neoadjuvant therapy with cetuximab alone or in combination with platinum salt and 5-FU have been proposed as a valid option for locally advanced cSCC [34▪▪]. Cetuximab combined with radiotherapy have also shown interesting results in terms of response rate, disease-free survival and overall survival [35,36]. Data on combination therapies are reported in Table 1. Panitumumab demonstrated responses in locally advanced cSCC in a phase II study [43]. This treatment has also been employed with success in the case of anaphylaxis after cetuximab [44].

Oral agents targeting the EGFR pathway include gefitinib and erlotinib. Gefitinib, which affects the ATP-binding site of EGFR, inhibits autophosphorylation and receptor activation. A small phase II neoadjuvant study in patients undergoing resection or radiotherapy demonstrated responses [complete and partial responses (PRs) of 18.2 and 27.3%, respectively] [45]. Treatment with gefitinib appeared well tolerated prior to surgery or combined with radiotherapy, but the role in this context is unclear. Similarly, erlotinib, another orally available EGFR inhibitor, demonstrates responses in advanced cSCC either alone [46] or in combination with other therapies [47,48▪▪,49].

EGFR pathway inhibition is generally well tolerated but generally results in modest disease control in a fraction of patients measured in months [30]. Resistance to EGFR inhibition develops relatively rapidly. The latter may result from several different mechanisms, including increased expression of EGFR, human epidermal growth factor receptor 2 and 3, insulin-like growth factor 1 receptor and tyrosine-protein kinase Met [50]. A mutation in *EGFR* gene resulting in the substitution P753S and activation of the EGFR kinase domain has been regarded as a biomarker of resistance. Although EGFR expression by tumor cells has been correlated inversely with clinical outcome [51,52], the degree of overexpression does not seem to correlate with the effectiveness of EGFR inhibitors. Better understanding of the EGFR pathway is expected to provide insights useful to design new trials.

OTHER SIGNALING PATHWAYS AND PHARMACOLOGICAL INHIBITORS

A recent gene set enrichment analysis has highlighted a key role for the MAPK pathway in cSCC [53]. A significant subset of patients treated with either the multikinase inhibitor sorafenib or the BRAF V600E inhibitors vemurafenib and dabrafenib rapidly develop cSCC [54]. Evidence exists indicating that these inhibitors result in a paradoxical activation of the MAPK pathway, which in turn cooperate with mutations in other key oncogenes and tumor suppressors such as H-RAS and TP53 [55]. Hence, it is likely that inhibition of the MAPK pathway provides a potential approach to treat cSCC.

Table 1. Survey of combination therapies with cetuximab for advanced cutaneous squamous cell carcinoma

Reference	Sample size	Outcomes	Comments
Acevedo-Henao *et al.* [37]	36	Complete remission 74%, partial remission 17% and OS 44.4%	Cetuximab induction followed by weekly maintenance until week 7 together with radiotherapy
Okano *et al.* [38]	22	Partial remission 82%	Cetuximab with concomitant boost radiotherapy in treatment-naïve SCC for 7 weeks
Knoedler *et al.* [39]	84	Partial remission 11%, stable disease 50%, median OS 6.7 months	Cetuximab with docetaxel in recurrent and/or metastatic SCC of the head and neck
Bossi *et al.* [40]	31	Well tolerated, improved compliance	Cetuximab as maintenance after induction with chemotherapy
Matuschek *et al.* [41]	55	Maintenance feasible, with acceptable toxicity	Cetuximab maintenance (6 months) after adjuvant concurrent radiochemotherapy plus cetuximab
Strojan *et al.* [42]	30	OS 50%, disease-free survival 47%	Induction chemotherapy (docetaxel, cisplatin, 5-fluorouracil) followed by radiotherapy and weekly cisplatin and cetuximab

OS, overall survival.

ROLE OF IMMUNE SYSTEM IN CUTANEOUS SQUAMOUS CELL CARCINOMAS DEVELOPMENT AND IMMUNOTHERAPY WITH CHECKPOINTS INHIBITORS

As with most solid tumors, the role of tumor inflammation appears critical to promoting the development of cSCC and may control the growth of established tumors [56]. cSCC is particularly prevalent in patients with chronic sun-exposure as well as in immune suppressed patients, in whom there is up to a 100-fold increased risk of developing cSCC compared with the general population [57,58,59▪,60,61]. Chronic UV exposure results in induction of suppressor T cells and depletion and down-regulation of Langherans cells [62,63]. The tumor microenvironment of cSCC is characterized by a reduced number of peritumoral $CD8^+$ cells [64] and increased number of regulatory T cells. Presence of tumor-associated macrophages, IL-10, transforming growth-beta and vascular endothelial growth factor all likely contribute to the immune dysfunction and tumor growth [65–67]. Finally, topical application of imiquimod, which activates toll-like receptors 7 on plasmacytoid dendritic cells, results in secretion of proinflammatory cytokines [68,69] and regression of squamous precancerous lesions [70].

All these observations provide strong rationale for the use of immunotherapy for advanced cSCC. Specifically, checkpoints inhibitors, which are able to activate a T-cell-specific immune response, have shown antitumor activity in different malignancies including malignant melanoma, non small-cell lung cancer and head and neck SCCs [71,72]. However, there are almost no data regarding the use of either the anti-CTLA4 antibody ipilimumab or anti-PD-1 agents, such as nivolumab or pembrolizumab, for cSCC [73▪,74▪▪].

Since the first positive observation in a 72-year-old patient with metastatic cSCC and melanoma, in which four cycles of ipilimumab resulted in clinical benefit and durable remission with a progression-free survival of 8 months, there have been other single case reports of adaptive immunotherapy in the form of anti-PD-1 for advanced unresectable or metastatic cSCC (Table 2). We have used anti-PD-1 inhibitors as rescue therapy in five cases with progressing advanced cutaneous squamous cell or basosquamous carcinoma. Our heavily pretreated patients with refractory tumors were given either nivolumab or pembrolizumab and showed clinical benefit including PRs and stable disease. Noteworthy in two cases with PR to anti-PD-1 inhibitors, PD-1L expression failed to reliably predict response. Anti-PD-1 therapy was well tolerated despite multiple comorbidities, including HIV infection. These findings are in line with the reported favorable side-effect profile of anti-PD-1 inhibitors. These observations suggest that immune checkpoint inhibitors may represent a promising new treatment option for aggressive cSCC. Controlled studies are

Table 2. Immunotherapy protocols encompassing immune checkpoint antibodies for treatment of advanced cutaneous squamous cell carcinoma

Reference	Cases	Treatment	Drugs	Outcomes	Progression-free survival	Significant adverse events
Day *et al.* [73▪]	Lung and liver metastatic SCC	Third line	Ipilimumab	PR	8 months	Hypophysitis
Winkler *et al.* [74▪▪]	Lymph node metastatic SCC	First line	Pembrolizumab	PR	5 months	None
Chang *et al.* [75▪▪]	Locally advanced SCC	Second line	Pembrolizumab	PR	5 months	Fatigue, weight loss and arthralgias
Lipson *et al.* [76▪▪]	Kidney-transplanted patient	Second line	Pembrolizumab	PR	8 months	Allograft rejection
	Metastatic SCC					
Borradori *et al.* [77▪▪]	Metastatic SCC	Third line	Pembrolizumab	PR	7 months	Fatigue, brain edema
	Locally advanced SCC	Fourth line	Pembrolizumab	Stable disease	4 months	None
	Locally advanced SCC	Second line	Nivolumab	PR	7 months	None
	Metastatic SCC	Fourth line	Nivolumab	PR	6 months	Fatigue, weight loss, hyponatremia

PR, partial response.

now planned to define the role of checkpoint modulation in management of nonmelanoma skin cancers.

CONCLUSION

Advanced cSCC remains a challenging disease with poor clinical outcome. In cases of extensive disease with local invasion and/or metastasis, surgery, antineoplasmatic agents and/or radiotherapy are often of limited value and efficacy. Comprehensive genomic profiling with identification of genomic targets and characterization of immunological pathways involved in cSCC development are currently providing the rationale for the development of novel targeted therapies and immunotherapies. The final goal is to optimize clinical outcomes through the effective personalization of treatment.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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