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SKIN CANCER (E TONGDEE AND O MARKOWITZ, SECTION EDITORS)

Advanced Squamous Cell Carcinoma: What's New?

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Abstract

Purpose of Review Advanced cutaneous squamous cell carcinoma (cSCC), though rare, is fatal with an 89% 5-year mortality rate. The diagnostic criteria for advanced basal cell carcinoma were recently redefined with the introduction of hedgehog inhibitors such as vismodegib. Similarly, the authors suggest redefining the diagnostic criteria of advanced cSCC given the introduction of immune checkpoint inhibitors in order to broaden the patient population that can benefit from both new and old treatment options as potential neoadjuvants.

Recent Findings Cemiplimab is a programmed death-1 (PD-1) inhibitor recently FDA-approved in 2018 for advanced cSCC with improved response rates (47–50%) compared to prior treatments. Given the lack of standardization, we suggest the diagnostic criteria of advanced cSCC to consider the patient condition, age, comorbidities, immunosuppression, and cosmetic outcome when determining a treatment regimen. Patients with diffuse cSCC due to immunosuppression may benefit from acitretin, while lesions on the lip may have a poor cosmetic outcome with surgery and may benefit from neoadjuvant therapy.

Summary Advanced cSCC does not have standardized diagnostic criteria likely due to the lack of treatment options until now. Additional treatment options may be beneficial to a broader patient population when redefining advanced cSCC to include factors such as immunosuppression and cosmetic outcome from the perspective of the patient.

Keywords Advanced cutaneous squamous cell carcinoma · Programmed death-1 inhibitor · Checkpoint inhibitor · Diagnostic criteria

Introduction

Squamous cell carcinoma (SCC) is the second most common skin cancer and accounts for 20% of all cutaneous malignancies, or 1 million cases in the USA each year [1]. SCC is the most commonly diagnosed skin cancer in darker skin types and is more likely to present at a more advanced stage [2, 3]. Risk factors for developing cutaneous SCC (cSCC) include advanced age, chronic exposure to ultraviolet radiation (UVR), UVR-sensitive skin, X-ray radiation, chemical exposure (e.g., arsenic or polycyclic hydrocarbons), and immunosuppression [4]. Invasive cSCC is defined histologically as the presence of infiltrative cells passing through the basement membrane into the dermis [5]. Surgical excision is the treatment of choice for invasive cSCC and is greater than 95% curative [4, 6]. In a limited number of cases, where surgery may not be possible, other options include topical therapies or destructive therapies such as radiotherapy, cryotherapy, curettage and electrodessication, or photodynamic therapy [4].

A minority of patients with invasive cSCC may be incurable due to metastasis or local progression unamenable to surgery or radiation therapy [7••]. These patients are considered to have advanced cSCC and palliative systemic therapy should be considered [7••]. Though only 5% of cSCCs become locally advanced, recur, or metastasize, the fatality rate is 1–5% (about 9000 deaths annually in the United States) for this subset of patients [8•, 9]. The presence of metastasis provides a poor prognosis with a median survival of less than 2 years, with one study showing an 89% mortality rate at 5 years for distant metastases [4]. This article discusses new

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treatments for advanced cSCC and whether a new definition for the disease entity should be considered, using a previously proposed definition for advanced basal cell carcinoma (BCC) for comparison.

Programmed Death-1 Inhibitors

Cemiplimab is a new systemic therapy that was FDA-approved in September 2018 as the first treatment for advanced cSCC [10]. Cemiplimab is a human monoclonal antibody that targets PD-1 with high affinity and high potency [11]. PD-1 plays a role in the immune response to cancer and can be found on white blood cells such as macrophages and lymphocytes [12, 13•]. Tumor cells bind to PD-1 using programmed cell death ligand-1 (PDL-1) and programmed cell death ligand-2 (PDL-2) to prevent an immune response from being mounted [12, 13•]. Cemiplimab prevents this binding of tumor cells to PD-1 [12, 13•].

A recently published study reported results of phase I and II trials of cemiplimab in adult patients with advanced cSCC. The expansion cohort of the phase I trial included 26 patients aged 55 to 88 years (median 73) with locally advanced cSCCs that had not responded to radiation or prior systemic therapy. Participants were eligible for inclusion in the study if they were not candidates for surgery due to (a) disease recurrence after two or more surgical procedures with expectations that curative resection would be unlikely or (b) surgery was anticipated to result in substantial complications or deformities [7••]. The phase I study showed a 50% (13/26) response rate for advanced cSCCs.

The phase II trial included 59 patients aged 38–93 (median 71) with distant or regional metastases and showed a 47% (28/59) response rate for metastatic cSCC [7••]. Cemiplimab was dosed at 3 mg/kg every 2 weeks for 48 weeks and 96 weeks in phase I and II studies, respectively [7••]. Safety data was evaluated in 534 patients. The most common adverse reactions were fatigue, rash, and diarrhea. Serious adverse events, while rare, were infusion reactions and immune-mediated reactions (e.g., pneumonitis, nephritis, hepatitis, colitis, and endocrine abnormalities).

Prior Treatments

Prior to cemiplimab, treatment options for cSCC included chemotherapy with platin derivatives and EGFR inhibitors. Chemotherapy such as cisplatin or carboplatin was considered the first line for advanced cSCC but had limited clinical data [14•]. Certain criteria such as advanced age, poor overall condition, or comorbidities may disqualify chemotherapy as an option [8•]. In these cases, EGFR inhibitors could be considered such as cetuximab and panitumumab. One study of cetuximab showed disease control in 69% of patients with 2 complete remissions and 8 partial remissions [15]. Oral EGFR inhibitors are another option, such as gefitinib which has shown a complete response rate of 18.2% and a partial response rate of 27.3% when used as a neoadjuvant [16]. A key issue with EGFR inhibitors is the frequent resistance that occurs [8•]. However, as with chemotherapy, clinical data is limited to EGFR inhibitors [8•]. Despite having these treatment options, there is currently no standard for the management for advanced cSCCs [8•]. Given the poor evidence and efficacy of the aforementioned treatment options, cemiplimab is an appealing new option given that it is the first systemic medication specifically tested for cSCCs while providing an improved efficacy rate of 47–50% as compared to previously available medications [7••]. Table 1 reviews treatment options for advanced cSCC.

Redefining Advanced cSCC

Advanced BCCs were recently redefined to address the lack of standardized criteria with the purpose of expanding the limited treatment options available for this small subset of patients [17, 18]. Redefining advanced cSCC should be considered for similar reasons. Lear et al. expanded the definition of advanced BCC to "basal cell carcinoma of American Joint Committee on Cancer (AJCC) stage II or above, in which current treatment modalities are considered potentially contraindicated by clinical or patient-driven factors." [18] Disease factors included tumor size, location, number of tumors, subtype, and likelihood of successful treatment (e.g., recurrent BCC) while patient factors included age (e.g., radiotherapy in young patients), performance status (e.g., frail patients), quality-of-life effects (e.g., poor cosmetic outcome), patient opinion of the treatment, presence of genodermatoses (e.g., Gorlin's syndrome), and comorbidities (e.g., organ transplant) [18]. Vismodegib was subsequently discussed in another article regarding its potential uses within this new definition of advanced BCC, both as a neoadjuvant to improve cosmetic outcome prior to surgery and as an adjuvant to decrease treatment duration and therefore minimize adverse events [17].

Similarly, advanced cSCC has not yet been redefined although it also lacks standardized criteria. Given its first FDA-approved medication (cemiplimab) was released onto the market, it would be prudent to propose a new definition to help determine which patients are amenable to this treatment. While surgery and a combination of chemotherapy and radiation therapy have been considered the gold standard, other factors such as the general condition of the patient, age, comorbidities, and immunosuppression should be considered as with advanced BCCs [19]. The definition of advanced BCC is relatively new (2014); given the rarity of advanced BCC and cSCC, as well as the recent development of hedgehog

Table 1 Medications for advanced SCC

Medication (route)	Indication	MOA	Efficacy and time to response	SE profile*	Year came to market
Platinum derivatives					
Cisplatin or carboplatin (used in combination with doxorubicin, 5-fluorouracil, and/or bleomycin, also used with concurrent radiation)	- Advanced testicular cancer - Advanced bladder cancer - Advanced ovarian cancer	DNA cross-linking	Overall response of 45% (22% complete + 23% partial) [26]	Short term: nausea and vomiting, leukocytopenia, anorexia, anemia, alopecia Long term: peripheral neuropathy can be irreversible Serious: nephrotoxicity, myelosuppression, peripheral neuropathy	1978 Off-label use for advanced cSCC
EGFR inhibitors					
Cetuximab (IV)	- Head and neck SCC - Colorectal cancer	Monoclonal antibody to EGFR	11% response rate at 6 weeks; up to 28% [15]	Short term: acneiform rash (usually after 2–3 treatments [3]), fatigue, nausea, constipation, dyspnea, sensory neuropathy, diarrhea, vomiting, headache, photosensitivity Long term: none specified Serious: infusion reactions, cardiopulmonary arrest	2004 for head and neck SCC Off-label use for surgically unresectable locally advanced or metastatic cSCC
Panitumumab (IV)	- Wild-type *RAS* colorectal cancer	EGFR antagonist	31% response rate; 69% disease control rate (response or stable) at 6 weeks [27]	Short term: rash, paronychia, fatigue, nausea, diarrhea, mucositis Long term: none specified Serious: infusion reactions, dermatologic toxicity	2006 for colorectal cancer Off-label use for locoregionally advanced or recurrent disease
Gefitinib (PO)	- Metastatic NSCLC with EGFR mutations	Tyrosine kinase inhibitor acting on EGFR	16% response rate among patients with locally advanced disease; 35% stable disease at 8 weeks [28]; 45.5% response rate and 22.7% stable disease as early as 2 weeks (mean 47.9, range 14–76 days) [16]	Short term: diarrhea, rash, nausea, vomiting, pruritus, anorexia, eye irritation Long term: none specified Serious: interstitial lung disease [16, 28, 29]	2015 for NSCLC Off-label use for incurable recurrent or metastatic disease cSCC
Erlotinib (PO)	- Locally advanced or metastatic NSCLC - Locally advanced, unresectable, or metastatic pancreatic cancer	Tyrosine kinase inhibitor acting on EGFR	10% partial response rate and 62% stable disease after 4 weeks; median duration of treatment was 98 days (range 1–526 days) [30] can get a response as early as 2 weeks [31]	Short term: acneiform rash, fatigue, diarrhea, anorexia, nausea, vomiting, mucositis, shortness of breath, cough [30–32] Long term: persistence of short-term side effects Serious: interstitial lung disease, liver and kidney failure, bullous skin disease, GI perforation, MI, CVA, clotting abnormalities, corneal ulceration	2004 for advanced NSCLC and pancreatic cancer Off-label use for metastatic or recurrent cSCC
PD-1 inhibitor					
Cemiplimab (IV)	- Metastatic SCC - Locally advanced SCC on patients who are not candidates for curative radiation or surgery	Programmed death-1 inhibitor (checkpoint inhibitor)	47–50% response rate with time to response median 1.9–2.3 months in phase 1 and phase 2 trials (range 1.7–7.3 months [7])	Short term: fatigue, nausea, diarrhea, constipation, hypophosphatemia, hypercalcemia, UTI Long term: none reported (phase 1 median follow-up 11.0 months (range 1.1–17.0); phase 2 median follow-up 7.9 months (range 1.1 to 15.6)) [7] Serious: cellulitis, pneumonitis, hypercalcemia, pleural effusion, death	2018

*The majority of trials did not report on time of onset of severe side effects

inhibitors (HHi) and PD-1 inhibitors, perhaps it was felt there was no need to define advanced disease until recently. Though the 5-year survival rates for BCCs and SCCs are comparable (10% and 11%, respectively), the more severe side effects of HHi for advanced BCC are mild (myopathies, alopecia, dysgeusia) compared to checkpoint inhibitors such as PD-1inhibitors for advanced cSCC (immune-mediated reactions) [4, 7••, 20, 21]. This stark contrast in side effects may have further contributed to a delay in, or perhaps even prevented, the broadening of criteria to diagnose advanced cSCC.

In Lear et al.'s expanded criteria of advanced BCC, they included genodermatoses such as Gorlin's syndrome as a patient factor to consider during diagnosis [18]. Though recurrent BCCs are difficult to manage and require multiple operations, this may not be feasible in patients with genodermatoses yielding multiple lesions, and radiotherapy may be contraindicated due to a high risk of developing further BCCs [22]. Similarly, immunosuppressed patients (e.g., post-transplant/chemotherapy) can develop a multitude of cSCCs and should be considered their own category among advanced cSCCs requiring their own management. For example, multiple studies of acitretin have shown efficacy in preventing cSCC in immunocompromised post-transplant patients [23–25].

A broadened definition of advanced cSCC should also include lesions in the H-zone. Markowitz et al. discussed facial BCCs which may be small but not considered advanced by the old definition. Though lesions in the H-zone may be small, they are considered to be in a high-risk area though amenable to surgery. This may cause a less ideal cosmetic outcome, especially if the lesion were to be on the lip. The same principles should apply to advanced cSCC, which if on the lip might require a wedge excision otherwise. Treatment options for advanced disease were limited until HHi were introduced, and now with cemiplimab, cSCC may be treated while keeping both disease and patient factors in mind. Similar to how vismodegib has been combined with imaging to monitor lesion size prior to surgery, cemiplimab could also be used as a neoadjuvant to decrease the cosmetic impact of therapy. While PD-1 inhibitors have early immune-mediated side effects, broadening the definition of SCC can be helpful when considering other safer treatment modalities such as neoadjuvants.

Conclusions

We propose adding certain subsets of patients to the definition of advanced cSCC including immunosuppressed patients and lesions cosmetically unamenable to surgery due to location. With the introduction of cemiplimab as the first FDA-approved medication for advanced cSCC, an expansion of diagnostic criteria opens up treatment options to a broader population. Certain patients may also require different approaches such as the use of acitretin in immunosuppressed patients. As new treatments unfold for rare but fatal diseases, we should continue to re-evaluate how we diagnose and manage patients.

Compliance with Ethical Standards

Conflict of Interest Orit Markowitz received payment from Regeneron for PD-1 inhibitor consultations.

Emily Tongdee, Corinna Psomadakis, Nadeem Marghoob, and Pavan Paka declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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