



Cutaneous squamous cell carcinoma

Risk factors and new systemic treatment options in advanced disease

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Summary Cutaneous squamous cell carcinoma (cSCC) accounts for approximately 20% of all skin cancers. Its rising incidence represents a major public health concern. The majority of cSCC are curable by surgical resection. Although less than 5% of cSCC patients develop metastases or local recurrence after complete excision, advanced cSCC is difficult to treat. Until recently, no standard therapeutic regimen for advanced cSCC exists. Traditional therapies include chemotherapy and EGFR-targeted therapy, but their clinical benefit remains modest and has been demonstrated mostly in retrospective studies. On the contrary, PD-1 inhibitors dramatically improve outcomes in many immunocompetent cSCC patients, resulting in the approval of cemiplimab as the first FDA-approved systemic drug for patients with locally advanced or metastatic cSCC who are not candidates for curative surgery or radiation. In the coming years combination therapies are an emerging treatment strategy that could improve efficacy of PD-1 inhibitors in advanced cSCC. Moreover, several prospective controlled trials have been designed to explore the potential role of PD-1 inhibitors in the adjuvant and neoadjuvant setting. Given the paucity of data, the management of immunocompromised cSCC patients requires a heightened awareness in this new era of cancer therapeutics.

Keywords Non melanoma skin cancer · Immunotherapy · Checkpoint inhibitors · PD-1-inhibitors · Organ transplant recipients

Introduction

Cutaneous squamous cell carcinoma (cSCC) accounts for approximately 20% of all skin cancers and is after basal cell carcinoma (BCC) the second most frequent form of nonmelanoma skin cancer (NMSC) [1]. The incidence of NMSC continues to rise since 1960 [2] and represents a major challenge for healthcare systems [3].

cSCC occurs predominantly on sun-exposed skin sites and is associated with high cumulative UV doses [4]. Phenotypic traits to develop cSCC are light hair, skin and eye colour [4]. Further major risk factors include older age [4] and immunosuppression [5]. It has been shown that white transplant recipients have a 65-fold higher risk of cSCC compared with the nontransplanted population [5]. The risk of developing cSCC is also increased in patients suffering from human immunodeficiency virus infection (HIV) and haematological diseases like non-Hodgkin lymphoma and chronic lymphatic leukaemia [4].

In most cases cSCC has a good prognosis and is curable by surgical resection. Nevertheless, a small percentage of patients progress to locally advanced or to metastasizing carcinoma [6]. A metastatic rate of 1.9–2.6% has been reported [7]. Regional lymph nodes are affected in approximately 85% of all cases, whereas the lungs, liver, brain and bones are less common sites of metastasis. The 10-year survival rates fall to less than 20% in case of locoregional lymph node metastases and less than 10% in the presence of distant metastases [6].

Risk factors for developing advanced cSCC are summarized in Table 1. Especially long-lasting and intense

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Table 1 Risk factors for developing advanced cSCC

High-risk factors in cSCC
Tumour size (diameter) >2 cm
Depth of invasion \geq 6 mm
Tumour site on ear, lip or areas of long-lasting chronic ulcers or inflammation
Acantholytic, spindle cell or desmoplastic histological subtype
Perineural involvement
Host immunosuppression
Recurrent lesions
Adapted from [4] and [10]

immunosuppression can induce rapid tumour growth and increase the probability for local recurrence and metastatic spread [8, 9]. Other risk factors associated with poor outcome have been identified, including large tumour diameter, lesion thickness, poor histological differentiation, location on the ear or lip and perineural involvement [4, 10].

There is no recommended standard therapeutic regimen for advanced cSCC and the number of randomized controlled trials are limited [10]. Radiotherapy \pm chemotherapy is considered as a conventional option for locally or regionally advanced disease [10–12]. Systemic chemotherapy and EGFR-targeted therapy are traditionally applied in patients with distant metastasis [10]. The use of chemotherapy has been explored mainly through retrospective studies and case series [10]. Reported overall response rates (ORR) with platinum monotherapy ranged from 17% to 78%, albeit these responses were typically short-lived and overall survival was not substantially extended [13]. ORR higher than 80% have been reported to polychemotherapy with cisplatin in combination with 5-fluorouracil and/or bleomycin [13, 14], but these results were only transient and not confirmed by subsequent studies [10]. Moreover, the toxicity profile of polychemotherapy precludes its use in a largely geriatric patient population with pre-existing comorbidities [10]. The EGFR-inhibitor cetuximab is preferentially used as subsequent line treatment when chemotherapy is unfeasible or there is a progressive disease [10]. In a phase II clinical trial cetuximab showed an ORR of 28% and a median progression-free survival (PFS) of 4.1 months with less toxicity in patients with locally advanced and metastatic cSCC [15]. In smaller studies higher ORR could be achieved when combined with chemotherapy and/or radiotherapy. Yet, median PFS remained still short in most cases [16].

Recently, data of 190 unselected patients with advanced cSCC who were diagnosed between 2010 and 2011 in Germany and Austria were analysed retrospectively with regard to patient profiles and treatment patterns, thus reflecting real-life conditions. In all, 40% of the patients suffered from locally advanced and 60% from metastatic cSCC. Only 32 patients, 3 with locally advanced and 29 with metastatic cSCC,

were treated with systemic antitumour regimens, in most cases with EGFR-inhibitor based therapies. ORR was 26% and median duration of response was 5 months [17]. These data confirm that chemotherapy and EGFR-targeted therapy offer only modest clinical benefit. Hence, there is a critical unmet need for improved advanced cSCC treatment. Checkpoint immunotherapy represents a promising new treatment option for inoperable cSCC.

PD1-based immunotherapy—a new systemic treatment option in advanced cSCC

The blocking of the PD1/PD-L1 pathway can enhance T-cell-activity and consequently promote tumour immunosurveillance [18]. In the last few years, the checkpoint inhibitors have been highly discussed as a promising treatment option for patients with advanced cSCC. The critical role of the immune system in controlling the development and growth of cSCC is well-known as cSCC diagnosed in immunosuppressed organ transplant recipients is more likely to show unfavourable prognostic features and to metastasize [5, 8]. Furthermore, findings such as high UV-mutation burden, infiltration with lymphocytes and PD-L1 expression in high-risk disease strongly indicate that targeting the immune system with PD-1 inhibitors could be effective in advanced cSCC [19–21].

The first case reports documenting the efficacy of the PD-1 inhibitors pembrolizumab and cemiplimab in advanced cSCC were published in 2016 [22, 23]. In September 2018, the PD-1 inhibitor cemiplimab became the first FDA-approved systemic drug for patients with locally advanced or metastatic cSCC who are not candidates for curative surgery or radiation [24]. Approval in Europe followed in July 2019. The approval was based on the results of a combined phase I/II clinical trial involving 85 patients, 75 with metastatic disease and 8 with locally advanced disease [25]. Most had undergone previous treatments, including prior radiation therapy and chemotherapy. 81% of pretreatment tumour samples were positive for PD-L1 expression. The results showed a quick onset of the clinical response after about 2 months with an ORR of 50% and a durable disease control rate (DCR) of 65.4%. A partial response (PR) was observed in 24 patients and a complete response (CR) in 4 patients. Similar efficacy was observed in patients with regional metastatic disease and in those with distant metastatic disease. The ORR was clearly associated with the status of prior systemic treatments: patients without prior systemic treatment had an ORR close to 60% and those with prior systemic treatment had an ORR close to 40%. The median duration of response (DOR) had not been reached and the estimated PFS probability at 1 year was 53%, whereas the probability of survival at 1 year was more than 80%. Most of the adverse events related to treatment were grade 1 or 2. Serious adverse effects accounted for less than

Table 2 PD-1/PD-L1 based immunotherapy in advanced cSCC—ongoing clinical trials as listed on ClinicalTrials.gov [27]

NCT identifier	Study title	Phase	Status	Cancer type	Drug
NCT02760498	Study of REGN2810 in patients with advanced cutaneous squamous cell carcinoma	Phase 2	Recruiting	Advanced cSCC	Cemiplimab
NCT02964559	Pembrolizumab in patients with locally advanced or metastatic skin cancer	Phase 2	Recruiting	Advanced cSCC	Pembrolizumab
NCT03284424	Study of pembrolizumab (MK-3475) in adults with recurrent/metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced unresectable cSCC (MK-3475-629/KEYNOTE-629)	Phase 2	Active, not recruiting	Advanced cSCC	Pembrolizumab
NCT03834233	Nivolumab in patients with advanced cutaneous squamous cell carcinoma (CA209-9JC)	Phase 2	Recruiting	Advanced cSCC	Nivolumab
NCT03737721	The UNSCARRed study: unresectable squamous cell carcinoma treated with avelumab and radical radiotherapy (UNSCARRed)	Phase 2	Recruiting	Unresectable cSCC	Avelumab with radical radiotherapy
NCT03944941	Avelumab with or without cetuximab in treating patients with advanced skin squamous cell cancer	Phase 2	Recruiting	Metastatic cSCC	Avelumab, Cetuximab
NCT03082534	Pembrolizumab combined with cetuximab for treatment of recurrent/metastatic head and neck squamous cell carcinoma	Phase 2	Recruiting	Advanced HNSCC and cSCC	Pembrolizumab, Cetuximab
NCT03666325	Immunotherapy ± EGFR inhibitor in advanced/metastatic cSCC: tackling primary and secondary resistance (I-Tackle)	Phase 2	Not yet recruiting	Advanced cSCC	Pembrolizumab, Cetuximab
NCT04050436	Study evaluating cemiplimab alone and combined with RP1 in treating advanced squamous skin cancer (CER-PASS)	Phase 2	Recruiting	Advanced cSCC	Cemiplimab, RP1 (genetically modified herpes simplex type 1 virus)
NCT03901573	High-risk skin cancers with atezolizumab plus NT-17	Phase 1/2	Not yet recruiting	Advanced cSCC and others	Atezolizumab + NT-17 (recombinant human IL-7-hybrid Fc)
NCT03684785	Intratumoral AST-008 combined with pembrolizumab in patients with advanced solid tumours	Phase 1b/2	Recruiting	Advanced cSCC and others	AST-008 (TLR9 agonist SNA), Pembrolizumab
NCT02955290	CIMAvax vaccine, nivolumab, and pembrolizumab in treating patients with advanced non-small cell lung cancer or squamous head and neck cancer	Phase 1/2	Recruiting	Advanced cSCC of the head and neck and others	Recombinant human EGF-rP64K/montanide ISA 51 vaccine (CIMAvax) and Nivolumab or Pembrolizumab
NCT03871348	A first-in-human dose escalation and expansion study to evaluate intratumoural administration of SAR441000 as monotherapy and in combination with cemiplimab in patients with advanced solid tumours	Phase 1	Recruiting	Advanced cSCC and others	SAR441000, Cemiplimab
NCT03590054	A phase 1b dose escalation/expansion study of abexinostat in combination with pembrolizumab in patients with advanced solid tumour malignancies	Phase 1b/2	Recruiting	Advanced cSCC of the head and neck and others	Abexinostat, Pembrolizumab
NCT03773744	MG1-MAGEA3 with Ad-MAGEA3 and pembrolizumab in patients with previously treated metastatic melanoma or cutaneous squamous cell carcinoma (Pelican)	Phase 1	Not yet recruiting	Metastatic cSCC and others	Ad-MAGEA3, MG-1MAGEA3, Pembrolizumab, Cyclophosphamide
NCT04007744	Sonidegib and pembrolizumab in treating patients with advanced solid tumours	Phase 1	Not yet recruiting	Advanced cSCC of the head and neck and others	Sonidegib, Pembrolizumab
NCT03108131	Cobimetinib and atezolizumab in treating participants with advanced or refractory rare tumours	Phase 2	Recruiting	Advanced cSCC and others	Cobimetinib, Atezolizumab
NCT03565783	Cemiplimab in treating participants with recurrent stage III-IV head and neck squamous cell cancer before surgery	Phase 2	Recruiting	Advanced cSCC of the head and neck and HNSCC (neoadjuvant)	Cemiplimab
NCT03969004	Study of adjuvant cemiplimab versus placebo after surgery and radiation therapy in patients with high-risk cutaneous squamous cell carcinoma	Phase 3	Recruiting	High-risk cSCC (adjuvant)	Cemiplimab, Placebo
NCT03833167	Pembrolizumab versus placebo following surgery and radiation in participants with locally advanced cutaneous squamous cell carcinoma (MK-3475-630/KEYNOTE-630)	Phase 3	Recruiting	Locally advanced cSCC (adjuvant)	Pembrolizumab
NCT03057613	The addition of pembrolizumab to postoperative radiotherapy in cutaneous squamous cell cancer of the head and neck	Phase 2	Recruiting	High-risk cSCC of the head and neck (adjuvant)	Pembrolizumab
NCT03816332	Tacrolimus, nivolumab, and ipilimumab in treating kidney transplant recipients with selected unresectable or metastatic cancers	Phase 1	Recruiting	Metastatic cSCC and others	Nivolumab, Ipilimumab, Prednisolon, Tacrolimus

10%. The most common adverse events of any grade were diarrhoea (27%), fatigue (24%), nausea (17%), constipation (15%) and rash (15%). There were 4 reported deaths due to adverse events. Of note, none were immune-related. Despite the advanced age of the patients (median age of patients over 70 years) no new safety signals were reported [25], suggesting that high age does not influence the efficacy and safety of the immunotherapy although patients enrolled in clinical trials have usually a better performance status compared with real-world patients.

The importance of PD-1 inhibitors has been further supported by preliminary data of a phase II trial with pembrolizumab on 39 patients, naive of chemotherapy and of EGFR inhibitors, with unresectable and/or metastatic cSCC and a median age of 80 showing an ORR of 42% and a median PFS of 7 months. Baseline PD-L1 expression was positive in 58%. Reported adverse events were consistent with previous studies. There were no severe adverse events or immune-related deaths [26].

Great interest currently exists in ongoing clinical trials evaluating the efficacy of immune checkpoint inhibitors in unresectable cSCC, especially in combination with other treatment modalities [27], (Table 2). PD1 inhibitors are also tested in the adjuvant and neoadjuvant setting. Two phase III and one phase II clinical trial are evaluating adjuvant cemiplimab and pembrolizumab following surgery and radiation in patients with high-risk locally advanced cSCC (NCT03969004, NCT03833167, NCT03057613). The application of neoadjuvant cemiplimab is being investigated in a phase II clinical trial in patients with advanced resectable cSCC of the head and neck followed by definitive local surgery and radiation (NCT03565783) [27].

As mentioned, organ transplant recipients are much more likely to develop cSCC than the general population [5]. Unfortunately, data regarding safety and efficacy of immune checkpoint inhibitors in this population are lacking. Routinely, those patients are excluded from immunotherapy trials due to safety concerns. There is emerging evidence that these agents may lead to graft rejection although there are reports in which immune checkpoint inhibitors have been used without resulting in organ rejection [28, 29]. A recent review, which included 57 organ transplant recipients receiving immune checkpoint inhibitors, reported graft rejection in 37% of patients and death due to graft rejection in 14% [30]. Most deaths (51%) were related to progression of malignancy. The highest rejection rate was seen in patients with kidney transplants (40.1%), followed by liver (35%) and heart (20%) transplants. Interestingly, 52% of patients receiving nivolumab experienced graft rejection, in contrast with 25% receiving ipilimumab and 26.7% receiving pembrolizumab. Time from transplantation and choice of immunosuppression at the time of treatment with immunotherapy might

be important factors for the outcome [30]. Another study, presenting the largest single-centre cohort of organ transplant recipients being treated with checkpoint inhibitor therapy, reported graft rejection in 41% and death primarily from allograft rejection or rejection complications in 46% of patients. The median time to rejection was 21 days and rejection rates were similar for anti-CTLA-4 and anti-PD-1 therapy. Also, no association was observed between time since organ transplantation and frequency, timing or type of rejection [31]. These data indicate that further studies are clearly needed to delineate a subset of organ transplant recipients who might benefit from immunotherapy. In this respect, a phase I clinical trial is examining kidney transplant recipients with selected unresectable cancers including cSCC who are treated with tacrolimus, nivolumab and ipilimumab (NCT03816332) [27].

Take home message

A new era in the treatment of advanced cSCC has been paved by the approval of the PD-1 inhibitors cemiplimab and pembrolizumab. Clinical studies with PD-1 inhibitors led to dramatically improved outcomes in many immunocompetent cSCC patients. Questions to be answered in the coming years will be whether response rates can be further improved by combination therapies and whether PD1 inhibitors are also effective in the adjuvant and neoadjuvant setting. Additional critical questions include the usage of immune checkpoint inhibitors in immunocompromised cSCC patients who have the highest medical need for new therapeutic options.

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