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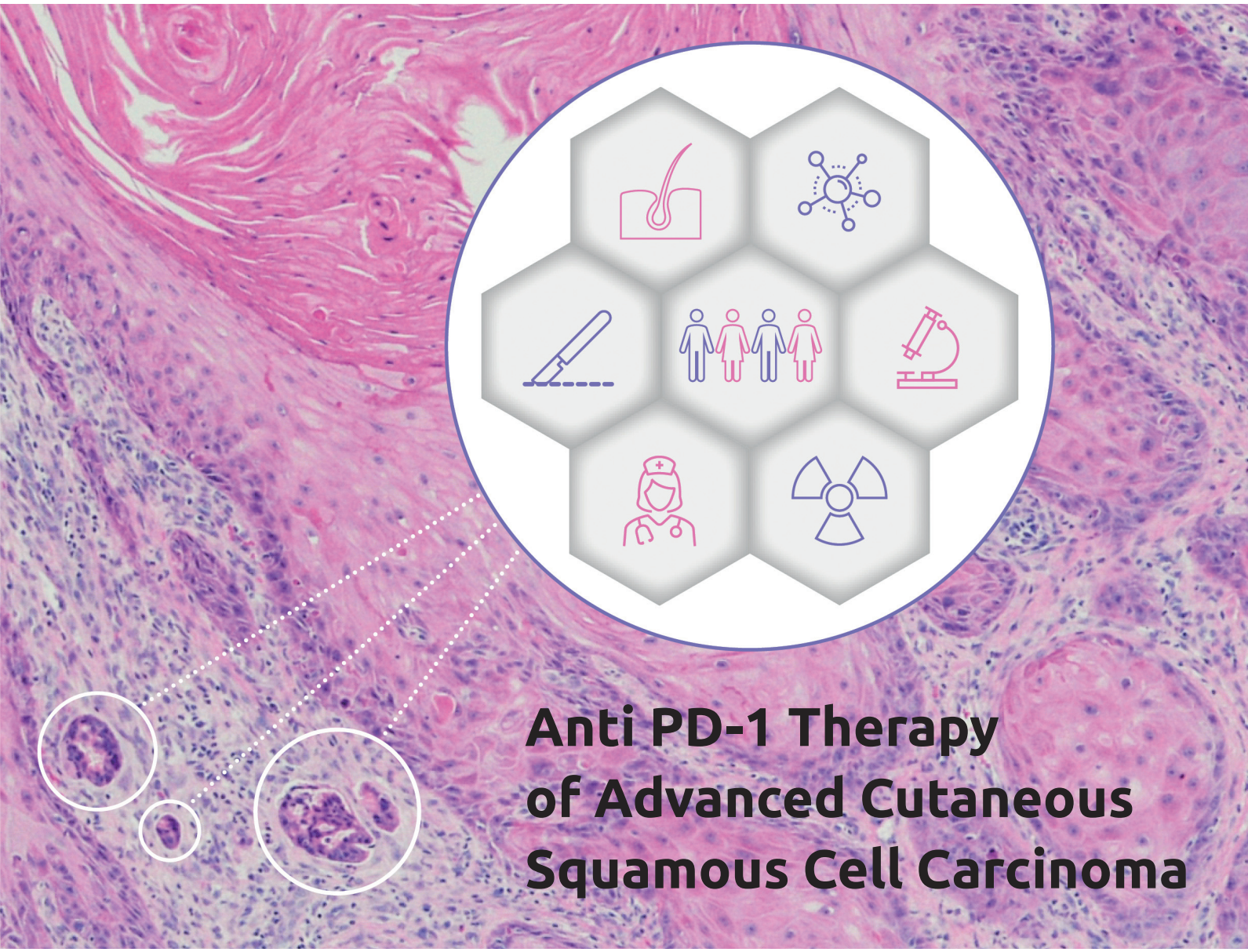

Anti PD-1 Therapy of Advanced Cutaneous Squamous Cell Carcinoma

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EDITORIAL

PD-1 – blockade in advanced cutaneous squamous cell carcinoma – fresh breeze in a deadly lull

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Opportunities come but do not linger. One such opportunity currently grasped like a straw is inhibition of T-cell checkpoint receptors in the care of patients with advanced solid tumours including skin cancer. Apart from CTLA-4 blockade, several anti-PD-1/PD-L1 antibodies have ushered in a revitalized era of cancer immunotherapy and dramatically shifted the landscape of treatment for cutaneous malignancies. Over the past years already, immune checkpoint inhibitors (ICI) became well-established first-line therapies in the fields of metastatic melanoma and Merkel-cell carcinoma. They definitely opened a window of opportunity to prevent fatal outcomes. Today, also patients suffering from advanced cutaneous squamous cell carcinoma (cSCC)[1] may benefit from this stimulating treatment strategy, explicitly the attempt to restore an effectual antitumour T-cell response through liberation from its receptor-mediated bonds. In the meantime, a wealth of important data and experience has cumulated not only from recent trial data but certainly also from practical application of ICI during every day clinical care. To provide a current state of the art, this supplemental issue of JEADV will exclusively deal with the management of patients suffering from advanced cSCC. Renowned experts in the field will highlight relevant therapeutic aspects in several review articles emphasizing the prospects and limits of checkpoint inhibition in that particular indication. In addition, they will discuss special treatment scenarios and exemplify distinct therapeutic challenges or individual particularities based on selected case reports.

Noteworthy, cSCC, together with basal cell carcinoma (BCC) also referred to as keratinocyte cancer, is the second most frequent skin cancer. It accounts for up to 20–25% of malignant epithelial skin tumours in fair-skinned populations. Due to an ongoing increase in life expectancy along with a steadily growing and probably still underestimated incidence rate, cSCC represents a significant burden to our healthcare systems.[2,3] Fortunately, the vast majority of invasive types of cSCC are diagnosed during early phases of development and frequently appear among several precancerous or in situ lesions in areas of field cancerization. Such cases receive standard surgical excision with an overall excellent prognosis, while initial in situ lesions including Bowen's disease can be targeted adequately by various lesion- or field-directed topical modalities.[4]

Difficult-to-treat situations, however, typically occur in elderly patients with neglected and locally progressed high-risk lesions, relevant multi-morbidities and/or physical or mental handicaps. They usually exhibit several features of high-risk SCC, both clinically and histologically. Particularly, in a growing high-aged male cohort with multiple and recurrent tumours developing within a field cancerization on their sun-damaged bald-headed and severely atrophic skin of the scalp, treatment can become a challenge. Complete surgical removal with respective safety margins or micrographic border control will often result in large defects with exposed underlying skull bone requiring extensive and demanding procedures for appropriate wound repair. In such situations, an effective and tolerable neoadjuvant approach would be desirable in an effort to either shrink larger tumour volumes prior to surgery or even replace the operation entirely. Likewise, the addition of adjuvant regimen to defeat recurrence and control concomitant areas of field cancerization is an interesting issue. In all of these scenarios, several trials are ongoing to examine both the preoperative and/or postoperative use of various anti-PD-1 checkpoint inhibitors. Phase II pilot studies NCT04315701 and NCT04154943 (R2810-ONC-1901) evaluate neoadjuvant use of cemiplimab in high-risk localized, locally recurrent and regionally advanced cSCC intravenously prior to surgery.[5,6] Phase 1 study NCT03889912 (R2810-ONC-1787) analysis preoperative cemiplimab administered intralesionally for patients with recurrent cSCC.[7] Two phase 3 trials (KEYNOTE-630 with pembrolizumab; R2810-ONC-1788 with cemiplimab) evaluate PD-1 blockade in an adjuvant setting after surgery and radiation therapy in high-risk locally advanced cSCC. Moreover, a German trial has been designed to evaluate effects of cemiplimab on actinic keratosis in patients treated for advanced SCC or metastatic SCC with co-existing field cancerization. In addition to cSCC and field cancerization, also BCC frequently occurring concomitantly in these skin cancer-prone individuals may benefit from PD-1 blockade, even after failure of hedgehog inhibitors in advanced stages.[8–10]

However, an even more challenging, albeit infrequent situation occurs in patients presenting with loco-regionally advanced

tumours not any more amenable to curative surgery or radiation therapy and in those with distant metastatic spread. Over decades, a poor outcome along with severely distressing toxicities was seen after various, mostly platinum-based (poly-) chemotherapies in the majority of such cases. The addition of antibodies and small molecules to target the epidermal growth factor led to better tumour control, particularly when combined with chemo- or radiotherapy. Yet, durable responses were not achievable, while patients suffered additional toxicities including those of the skin.[11,12] Perspectives changed entirely when ICI became available not only in the field of head and neck squamous cell carcinomas. Apart from immune cell infiltration or PD-L1 expression, also further UV-induced increase in mutational loads suggested their utility particularly in cSCC.[13–15] In fact, among several ICI under clinical investigation, intravenous fully human high-affinity IgG4 anti-PD1 monoclonal antibody cemiplimab has led to clinically significant objective response rates with durable efficacy and an acceptable safety profile in this indication.[16–19] Cemiplimab became the first approved treatment (FDA Sep/2018 and EMA June/2019) for both locally advanced cSCC and metastatic cSCC patients who will no longer benefit from curative surgery or curative radiotherapy. Phase 2 trials also demonstrated ongoing responses for pembrolizumab (FDA approval, June/2020), both in second- and first-line treatment.[20,21] Several ongoing studies evaluate combined usage of PD1-based checkpoint inhibition. Among these, a phase 1b/2 trial looks at pembrolizumab or cemiplimab in combination with intratumoural toll-like receptor 9 agonist cavrotolimod, while the CERPASS II trial investigates cemiplimab as a single agent and in combination with a genetically modified herpes simplex type 1 virus.[22,23]

Moreover, a growing number of immunocompromised individuals (patients with haematological malignancies, solid organ or autologous stem cell recipients) are candidates at risk to develop epithelial skin cancers. Particularly, solid organ transplant recipients do not only have an increased likelihood of developing multiple and recurrent cSCC but also tumours of a more aggressive behaviour with an overall higher occurrence of metastatic disease.[24,25] In fact, cSCC is the most common post-transplant neoplasm and even outnumbers BCC. However, organ transplant recipients had to be excluded from clinical trials because of potential graft rejection with ICI therapy. Meanwhile instead, PD-1 blockade is also evaluated in immunocompromised individuals under certain precautions, e.g. the utility of cemiplimab monotherapy in participants who have previously received an allogeneic hematopoietic stem cell transplant or kidney transplant along with immunosuppressant drugs to prevent kidney rejection (CONTRAC study).[26]

Finally, a current debate evolves about the safety of immune-stimulating treatments in the era of COVID-19 pandemic. Among concerns are those because of potential interference between autoimmune pneumonitis and viral pneumonia, but also in view of an accelerated and life-threatening cytokine storm.[27] However, ICI are usually not given during active COVID-19 disease or in any patients with flu-like symptoms. Noteworthy, patient data from COVID hotspot areas in Italy suggest the safety of continued use of PD-1 blockade during the pandemic.[28] However, due to being elderly and potentially affected by multiple comorbidities, such individuals may be at higher risk of bad outcomes from COVID-19 if infected, and also potential immune-related adverse events may be confused with COVID-19 symptoms.

Considering all these data from recent trials and practical clinical work in a today's perspective, the formerly discouraging scenery of treating advanced cSCC has taken on completely new contours and for the first time it opens up prospects for a better future. We expect our patients to benefit from further groundbreaking innovations with even more individualized choices already during this new decade. Unfortunately, not all individuals may profit from such windows of opportunity and a substantial percentage of responders will eventually relapse because of yet poorly understood reasons. Therefore, current and future work will have to define how we better can predict response and identify appropriate candidates. This also includes the search for overcoming potential mechanisms of acquired or intrinsic anti-PD-1 blockade resistance, and for combinatorial drug regimens.

Conflict of interest

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REVIEW ARTICLE

Update of advanced cutaneous squamous cell carcinoma

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Abstract The incidence of cutaneous squamous cell carcinoma (cSCC) is rapidly increasing. A growing part of this patient group is formed by immunocompromised patients, for example organ-transplant recipients (OTR). Although over 90% of the cSCC show a relatively harmless clinical behaviour, there is also a chance of developing advanced cSCC and metastases. Locally advanced cSCC are defined as cSCC that have locally advanced progression and are no longer amenable to surgery or radiation therapy. Better understanding of the clinical behaviour of cSCC is essential to discriminate between low- and high-risk cSCC. Staging systems are important and have recently been improved. Genetic characterisation of SCC will likely become an important tool to help distinguish low and high-risk cSCC with an increased potential to metastasise in the near future. Available treatments for high-risk and advanced cSCC include surgery, radiotherapy, chemotherapy and targeted therapy with epidermal growth factor receptors inhibitors. Anti-PD-1 antibodies show promising results with response rates of up to 50% in both locally advanced and metastatic cSCC but, in its present form, is not suitable for OTR.
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Introduction

Cutaneous squamous cell carcinomas (cSCC) are keratinocyte carcinomas, originating from the keratinocytes located in the epidermis or adnexal structures. They account for approximately 20% of all cutaneous malignancies. Although exact cumulative incidences are hard to estimate, a rising trend in cSCC is documented worldwide for decades.[1]

Risk factors for cSCC are increasing age, male gender, exposure to ultraviolet radiation (UVR), infection with β-human papillomaviruses (HPV), smoking, genetic factors (fair skin, genetic syndromes) and immunosuppression. In the context of organ transplantation, the immunosuppressive agents azathioprine and cyclosporin and the antifungal drug voriconazole are associated with an increased risk of cSCC.[2]

Although more than 90% of the cSCC display a relatively harmless behaviour, there is also a group of patients who develop advanced cSCC.[3] Advanced cSCC include locally advanced and/or metastatic cSCC. Locally advanced cSCC are defined as cSCC that have locally advanced progression (tumours that are large or have penetrated deep into underlying tissues, muscles or nerves) and are no longer amenable to surgery or radiation therapy. Metastatic cSCC are tumours that have spread beyond the original location to adjacent skin, lymph nodes or other organs.[4]

Better understanding of the clinical course of cSCC is essential to identify those cSCC that are prone to aggressive growth and/or metastatic behaviour. The immune system plays an important role in the development of cSCC. Organ transplant recipients (OTR) have a 60–100 times increased risk to develop cSCC compared to the age and sex matched immunocompetent population.[5] The number of immunocompromised patients worldwide is rising due to an increase in the number of organ transplantations but also the number of patients with inflammatory bowel disease and rheumatoid arthritis who are treated with immunosuppressive drugs for prolonged periods increases over time.[6,7]

Staging systems for cSCC are important and have been recently improved.[8] Genetic characterisation of cSCC with an increased potential to metastasise will possibly become an important tool to help us diagnosing cSCC with a poor prognosis in the near future.[9]

The relatively poor prognosis of locally advanced and metastatic cSCC emphasises the need for novel therapeutic strategies in this group. PD-1 inhibitors show promising results but may not be useful for cSCC in OTR, because of the increased risk of transplant rejection.

This review will give an update on the epidemiology, risk factors, staging systems and current treatment options of advanced

cSCC. Management of advanced cSCC in the immunocompromised population receives extra focus in this review.

Epidemiology and patient related risk factors associated with local recurrence and metastases

The risk of cSCC metastases varies between 0.1% and 9.9% in the immunocompetent population, with a 2.8% chance of dying because of this disease.[10] Most cSCC represent low-risk cSCC. However, high-risk cSCC may have a metastatic rate of up to 37%.[11] Approximately 90% of cSCC metastases appear within 2 years after the initial diagnosis.[12] More than two-third of the patients suffering from cSCC metastases die because of locally invasive cSCC or nodal metastases, rather than distant organ metastases.[13] Thompson *et al.*[14] published an excellent study regarding tumour related risk factors for recurrence, metastases and disease-specific death and a summary is displayed in Table 1.

It is expected that the risk factors for metastases are similar in OTR and the immunocompetent population, yet immunosuppressed patients with cSCC could have worse outcomes.[15] In one study, the metastatic rate of cSCC is estimated at 13% in the presence of immunosuppression[16]; however, a recent meta-analysis showed a pooled metastasis risk estimate of 7.3%.[17] Another study related the high metastatic rate of cSCC in OTR to the higher amount of local recurrences in OTR compared to immunocompetent patients.[18]

Better understanding of pathogenesis of high-risk cSCC

The influence of the immune system on the development of cSCC and cSCC metastases is still underreported and merits more attention.

In immunocompetent patients, the immune system is able to recognise antigens related to viral infections, as well as tumour antigens. This is called immune surveillance. Immunocompromised patients, for example OTR have an impaired immune surveillance due to their life-long immunosuppressive medication, which is needed to retain the transplanted organ, but thereby facilitating the survival and proliferation of atypical cells. The cSCC have a high mutational load with on average 50 mutations per megabase pair DNA.[19] This is even more than the average mutational load in malignant melanoma,[20] which should be sufficient to lead to frequent formation of neoantigens that can be recognised by T lymphocytes.[21] cSCC are, therefore, highly immunogenic tumours, which makes immunocompromised patients, especially vulnerable for developing cSCC.[22] An important defence line consists of elimination of altered cells by innate and adaptive arms of the immune system.[23] Antigens are secreted by tumour cells, will be expressed on the cell membrane and recognised by antigen presenting cells (APC). T lymphocytes and natural killer (NK) cells, among others, are then activated to help eliminate the tumour cells. The human leukocyte antigen (HLA) system has an important role in the recognition of antigens. HLA class I can be found on all cells in the human body. Its function is to present antigens to the CD8 positive T lymphocytes and to make connections with NK cells. HLA class II are expressed on APCs (dendritic cells, macrophages, B cells and CD4 positive T lymphocytes). HLA class III has involvements within the complement system and cytokine formation. When a T lymphocyte recognises the peptide presented by the HLA antigen in the tumour cell, co-receptors act as activators and inhibitors of the immune response (Fig. 1). Programmed cell death 1 protein (PD-1) and Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) are inhibitory receptors and known as immune checkpoint receptors. PD-1 is expressed on the surface of T cells, B cells, natural killer cells, dendritic cells and monocytes.

Table 1 Risk factors for recurrence or metastasis of cutaneous squamous cell carcinoma, adjusted from Thompson *et al.*[14]

Risk factors
Breslow thickness >2 mm
Invasion beyond subcutaneous fat
Perineural invasion
Diameter >20 mm
Poor differentiation
Immunosuppression
Location on the lip, ear or temple

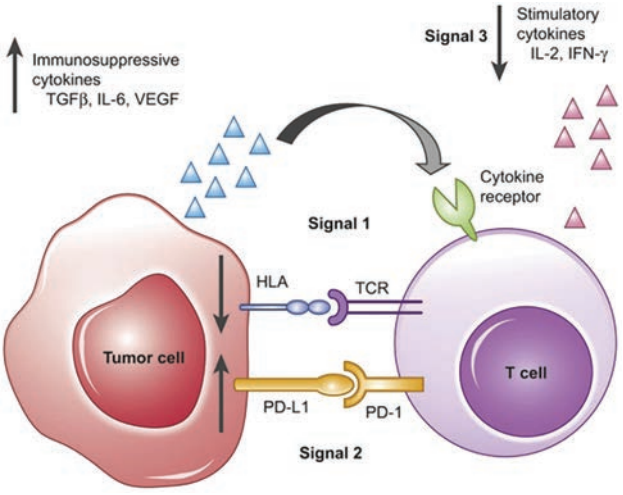

Figure 1 Immune surveillance. Reproduced from Moy *et al.*[46] with permission from Elsevier. T-cell activation requires three simultaneous signals in order to carry out its anti-tumour effects. Signal 1 comprises the T-cell receptor – HLA interaction, with presentation of antigens from the tumour cell. Signal 2 is a summation of costimulatory and coinhibitory signals. These signals must occur in the presence of Signal 3, made up of immune-activating cytokines, such as IL-2 or IFN-γ. Programmed cell death 1 protein (PD-1) is an inhibitory receptor. Immune evasion can occur at any of these signals (black arrows), impairing the immune system from effectively eradicating malignant cells.

UVR plays a key role in cSCC carcinogenesis by inducing DNA mutations and escaping from immune surveillance.[24] DNA mutations caused by UVR in skin cancers include inactivation of tumour suppressor genes (p53, CDKN2A and PTCH) or activation of proto-oncogenes (Ras). These genes are regulators of the cell cycle and when altered are able to induce tumorigenic effects. The accumulation of mutations ultimately involves various signalling pathways, which mediate epidermal growth factor receptor (EGFR) overexpression. These pathways include RAS-RAF-MEK-MAPK, PLC-gamma/PKC, and PI3K/AKT/mTOR and when altered, they can trigger increased proliferation, migration, survival, resistance to apoptosis and altered differentiation.[25]

UVR has also important effects on immune function and causes alterations of the cutaneous cell mediated immunity.[23] A decrease of function of the Langerhans cells, cytotoxic and helper T lymphocytes as they are depleted and may have undergone changes in morphology, and an simultaneous increase of UV-induced regulatory T cells lead to alterations in favour of both the development of skin tumours and a higher risk of metastasis. UV-mediated immunosuppression can be both local and systemic by secretion of immunosuppressive cytokines.[23] For example azathioprine and voriconazole are both photosensitive agents and as such can induce tumorigenic effects.

Chronic inflammation can also trigger certain molecular and cellular networks that have a role in the initiation and progression of cSCC, as well as tumour angiogenesis and metastasis.[26]

Infection with βHPV is thought to play a role in the initiation stage of cSCC carcinogenesis, although the opinions on this subject are controversial.[27] There is evidence that the processes of DNA repair and UVR-induced apoptosis are less effective in βHPV infected cells, which leads to accumulation of DNA damage with actinic keratoses, Bowen's disease and cSCC as the final end result. βHPV most likely does not play a role in the maintenance of the malignant phenotype or in the development of advanced stages of cSCC.[28]

Better identification of high-risk cSCC

The significant morbidity and mortality of patients with advanced cSCC highlights the urgent need for early identification of high-risk cSCC.

Multiple tumour classification systems have been developed in which various criteria are determined that carry a higher risk of locoregional or distant metastases. Commonly used classification systems are the American Joint Committee on Cancer (AJCC) tumour classification system, the Union for International Cancer Control (UICC) classification system and the Brigham and Women's Hospital (BWH) Tumour Classification System. Differences between the systems are displayed in table 2. In January 2018, the eighth edition of the AJCC (AJCC8) came into force.[8] Important changes compared to the seventh edition (AJCC7) were the following: SCC of the vermillion lip were categorised under cSCC instead of oral SCC. Risk factors for T1 to upstage to T2 were removed. Instead, risk factors as tumour invasion of >6 mm (instead of >4 mm) and/or invasion beyond the subcutaneous fat, and perineural invasion was defined as tumour cells in the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in calibre, were introduced to upstage a T1 or T2 tumour to T3. Well-known risk factors such as differentiation grade, angioinvasion and a location

Table 2 Changes between the American Joint Committee on Cancer (AJCC8), Union for International Cancer Control (UICC8) and Brigham and Women's Hospital (BWH) classification systems.[30,36]

AJCC8		UICC8		BWH	
T1	≤2 cm in greatest diameter	T1	≤2 cm in greatest diameter	T1	0 High-risk factors§
T2	>2–4 cm in greatest diameter	T2	>2–4 cm in greatest diameter	T2a	1 High-risk factors
				T2b	2–3 High-risk factors
T3	Tumour >4 cm in greatest diameter or minor bone invasion or perineural invasion or deep invasion†	T3	Tumour >4 cm in greatest diameter or minor bone invasion or perineural invasion or deep invasion‡	T3	≥4 High-risk factors
T4a	Tumour with gross cortical bone and/or marrow invasion	T4a	Tumour with gross cortical bone and/or marrow invasion		
T4b	Tumour with skull bone invasion and/or skull base foramen involvement	T4b	Tumour with skull bone invasion and/or skull base foramen involvement		

†Deep invasion defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour), perineural invasion defined as tumour cells in the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in calibre or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

‡Deep invasion defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumour); perineural invasion for T3 classification is defined as clinical or radiographic involvement of named nerves without foramen or skull base invasion or transgression.

§BWH high-risk factors include tumour diameter ≥2 cm, poorly differentiated histology, perineural invasion of nerve(s) 0.1 mm in calibre or tumour invasion beyond subcutaneous fat (excluding bone invasion, which upgrades tumour to BWH stage T3).

on the ear or lip do not contribute to the tumour, nodes, metastasis classification anymore. Recurrent cSCC and immunosuppression are often mentioned as risk factors for metastases; however, they are not yet incorporated in these staging systems.

The positive predictive value of the AJCC8 for a poor outcome remains only 17%[8,29,30] as the majority of cSCC designated 'high-risk' do not develop advanced disease, and does not allow accurate prediction of which cSCC will progress to locoregional spread or disease-specific death.[8,31,32] An alternative staging system from BWH performs better, but the positive predictive value for a poor outcome is still only 24%-38%.[8,30]

Staging systems for locally advanced cSCC have not been extensively studied. In staging systems for melanoma and Merkel cell carcinoma, it is known that in-transit metastasis has prognostic value; however, this is not yet incorporated in cSCC staging. A recent study compared the outcome of patients with cSCC in-transit metastases with T3N0 tumours, T4 tumours with bone invasion, lymph node metastases and distant metastases. cSCC patients with in-transit metastases experienced outcomes similar to locally advanced non-metastatic cSCC patients.[33]

Besides these clinical and histological characteristics, better understanding of the genomic alterations and the mechanisms of immune evasion that drive locally advanced and metastatic cSCC is urgently needed to provide more accurate predictive algorithms. Recently, a study was published in which a gene expression profile was developed and validated for predicting high-risk cSCC, showing a positive predictive value of 60% in the highest risk group.[9] Large-scale studies investigating genetic risk factors for cSCC metastases in OTR have not yet been performed.

Currently, lymph node palpation, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) are frequently used methods for detection of metastasis. Recent studies state that in patients with high-risk cSCC, in the cases of absence of clinically palpable lymphadenopathy and negative imaging, it would be reasonable to consider sentinel lymph node biopsy; however, convincing evidence is still lacking.[34,35]

Better treatment and prevention

Management of cSCC is important, especially in patients suffering from multiple cSCC. Surgery remains the golden standard for low-risk cSCC. The European consensus group suggests 6–10 mm clinical safety margins for cSCC with high-risk factors.[36]

The great advantage of Mohs' over traditional surgical excision is that 100% of the surgical margins can be evaluated, resulting in lower recurrence rates (3% vs. 8% during a follow-up period of 5 years, respectively).[37] However, it should be mentioned that no randomised controlled trials comparing Mohs' and standard surgical excision have been performed. One study found a 52% tissue-sparing effect for Mohs' vs. standard surgical excision.[38] When it is not possible to perform a re-excision in case of narrow margins, adjuvant radiotherapy can be considered. Curettage and electrodessication is a safe therapy for OTR suffering from multiple T1 cSCC (well differentiated tumours on low-risk locations) with a cure rate of around 95%.[39]

Locally advanced and metastatic cSCC require other treatments that need to be evaluated by a multidisciplinary team. Available treatment options include chemotherapy (such as cisplatin), targeted therapy with EGFR inhibitors (i.e. cetuximab) and anti-PD-1 antibodies (cemiplimab, pembrolizumab, nivolumab). Cemiplimab is the first systemic treatment approved by FDA and EMA for advanced and metastatic cSCC.[40] Anti-PD-1 antibodies show promising results with response rates of up to 50% in both locally advanced and metastatic cSCC,[41] with emerging evidence of durable responses.[42] The side effect profile of anti-PD-1 antibodies appears to be favourable compared to chemotherapy. PD-1 inhibitors may not be useful for cSCC in OTR, because of the high chance of transplant rejection.[43]

Education for prevention and early detection of cSCC is a corner stone for all OTR. The use of sun-protective closing, hats and sunscreens should be promoted. Prescription of systemic retinoids, nicotinamide and field treatments for actinic keratoses such as 5-fluorouracil should be discussed for high-risk patients.

Animal studies with an HPV vaccine have shown a protective effect against the development of cSCC in HPV infected animals, but an effective vaccine to protect against actinic keratoses and cSCC in human beings is currently not available.[44]

Reliable identification of the highest risk cSCC by gene expression profile could allow clinicians in the future to deploy more aggressive surgery and/or adjuvant radiotherapy for these tumours, thus reducing metastatic risk.[9,45]

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REVIEW ARTICLE

Overview of guideline recommendations for the management of high-risk and advanced cutaneous squamous cell carcinoma

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Abstract Cutaneous squamous cell carcinoma (cSCC) is the second most common form of skin cancer. National and international associations have issued evidence- and consensus-based guidelines to offer clinicians a framework to optimally manage patients with invasive cSCC. Current updated guidelines regarding the recommendations on the management of patients with high-risk and advanced cSCC include EDF/EADO (European) Guidelines 2020, US National Comprehensive Cancer Network guidelines 2021, American Academy of Dermatology guidelines 2018, British Association of Dermatology guidelines 2020 and German guidelines 2020. This review presents the guideline recommendations on the definition of high-risk and advanced cSCC, surgical treatment and safety margins, definitive and adjuvant radiotherapy and systemic treatments. The recommendations across guidelines may converge, diverge or in some cases not be able to provide a recommendation, highlighting open questions to be answered by future studies.
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Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common form of skin cancer, accounting for 20% of keratinocyte carcinomas.[1,2] The majority of patients with invasive cSCC have an excellent prognosis after surgical clearance.[3] For patients with CSCC, the risk of local recurrence (LR) is 2% and the risk of nodal metastasis (NM) is 5%.[4,5] Disease-specific death is estimated to be 1.5–2.1%.[5,6] A subset of cSCC, namely the high-risk cSCCs are associated with worse prognosis and up to 37% of high-risk cSCCs may progress to advanced cSCC.[7]

National and international associations have issued evidence- and consensus-based guidelines to offer clinicians a framework to optimally manage patients with invasive cSCC. This review presents current updated guidelines or recommendations for the management of patients with high-risk and advanced cSCC, including the European 2020,[8,9] US National Comprehensive Cancer Network (NCCN) 2021 version 1,[10] US American Academy of Dermatology (AAD) 2018,[11] British Association of Dermatology (BAD) 2020[12] and German 2020.[13]

Guidelines on the management of high-risk cSCC

High-risk cSCC is defined as invasive cSCC staged as N0 (without detectable regional lymph nodes) and M0 (without distant metastasis), which has features associated with a higher risk for local recurrence and metastasis.[7] The risk factors for local recurrence and metastasis may be classified as intrinsic (tumour-related) or extrinsic (patient- and physician-related). All five aforementioned guidelines include tumour clinical diameter (although different thresholds are proposed across guidelines), high-risk location (varying locations proposed across guidelines), vertical histological thickness (>6 mm), poor grade differentiation, desmoplasia and histological perineural invasion (PNI). Invasion beyond subcutaneous fat is a risk factors in all guidelines except German. Bone erosion is proposed by the European guidelines and bone invasion by the BAD guidelines. All guidelines include the patient-related high-risk factor of immunosuppression, while the European[8] and BAD[12] guidelines also include the extrinsic high-risk factor of the histological margin status. A higher risk for recurrence, metastasis and disease-specific death is further conferred by the number of high-risk

features present, as proposed by the Brigham and Women's Hospital (BWH) T classification system. In the BWH system, the combination of two or more high-risk factors (among clinical diameter ≥2 cm, PNI of ≥0.1 mm calibre, poor differentiation, and invasion beyond subcutaneous tissue) significantly increases the risk of negative outcomes and defines a high-stage cSCC (T2b, T3). Bone invasion upstages the tumour to T3.[4,14]

The therapeutic recommendations for high-risk cSCC by the European guidelines are summarized in Fig. 1.

Surgical treatment for high-risk cSCC

In all guidelines, surgical excision is considered the first-line treatment for resectable primary cSCC and aims at clinical and microscopic complete resection (R0 surgery) with clear (negative) histological margins.

Standard surgical excision with histological confirmation of peripheral and deep margins is the first-line treatment option for resectable primary cSCC. The European guidelines recommend standard excision and postoperative margin assessment or Mohs' micrographic surgery (MMS) for high-risk cSCC.[9] The NCCN guidelines recommend standard excision and postoperative margin assessment for high-risk cSCC, or MMS or resection with complete circumferential peripheral and deep margin assessment (CCPDMA), preferred for very high-risk cSCC.[10] In the AAD guidelines, MMS is recommended for high-risk csCC, and standard excision may be considered for select high-risk

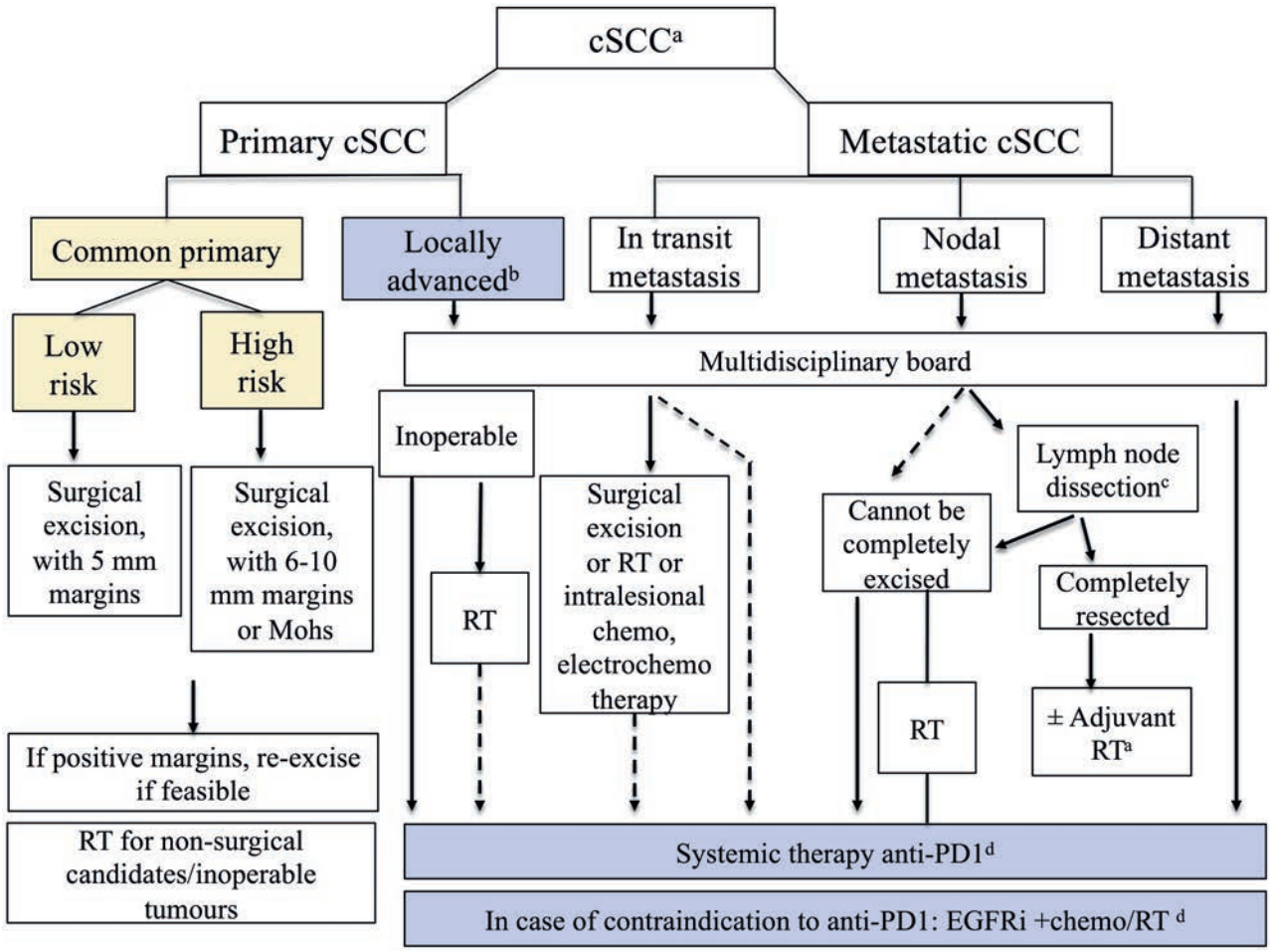

Figure 1 Main therapeutic indications for high-risk and advanced cutaneous squamous cell carcinoma (cSCC). (Reused from Stratigos *et al*.,[9] with permission). In addition, it is noted that since the publication of this figure, anti-PD-1 agent pembrolizumab has been approved by US FDA for patients with recurrent or metastatic cSCC that is not curable by surgery or radiation. EGFRi, EGFR inhibitors; La, locally advanced; RT, radiotherapy. [a]For detailed indications and recommendations of treatment, refer to relevant section text in the European Guidelines. [b]Locally advanced by definition not amenable to curative surgery or curative RT. [c]Lymph node dissection as indicated. [d]All systemic treatments are off-label, except for anti-PD-1 agent cemiplimab that is approved by FDA/EMA for patients with locally advanced or metastatic cSCC who are not candidates for curative surgery or curative radiation.

tumours.[11] In the BAD guidelines, it is recommended to offer standard surgical excision as first-line treatment for resectable primary cSCC and to consider Mohs micrographic surgery in selected cSCC following specialist skin cancer multidisciplinary tumour board meeting (SSMDT) discussion, particularly for cases with tumour margins that are difficult to delineate or in sites where tissue conservation is important for function.[12] The German guidelines recommend complete excision with histological evaluation of both peripheral and deep margins.[13]

In case of involved (positive) histological margins, a re-excision, if feasible, is recommended in all guidelines.

Regarding clinical safety margins for standard excision, the European guidelines suggest a 5-mm margin for low-risk cSCC and 6- to 10-mm safety margins for cSCC with high-risk factors.[9] The NCCN guidelines recommend 4- to 6-mm clinical margins for low-risk cSCC and wider margins for high-risk cSCC without further specifying, primary due to the wide variability of characteristics that may define a high-risk cSCC as well as underlying tumour or patient-specific factor.[10] The British guidelines recommend a clinical surgical margin of at least 4 mm for a low-risk tumour, 6 mm for high-risk cSCC and at least 10-mm clinical margins for very high-rsik cSCC.[12] The German guidelines do not provide a specific recommendation for safety margins.[13]

Sentinel lymph node biopsy

European guidelines do not recommend SLNB for cSCC outside of the setting of clinical trials.[8] NCCN guidelines recommend to discuss and consider SLNB in very high-risk cSCCs that are recurrent or have multiple risk factors and have normal examination of the draining nodal basin.[10] The AAD and German guidelines do not issue any recommendation as the value of SLNB for cSCC is unknown, and the BAD guidelines recommend to consider SLNB for specific, high-risk, primary cSCC in the context of a clinical trial/SSMDT.[11–13]

Primary definitive radiotherapy for high-risk cSCC

Definitive primary radiotherapy (RT) represents an alternative to surgery and effective curative treatment for small cSCCs. RT may be considered as a primary treatment in patients who are not candidates for surgery (e.g. locally advanced cSCC, presence of comorbidities or decline of surgery) or in cases where curative surgery is not possible or could be disfiguring or burdened by the poor functional outcome, especially cSCCs located on the face (i.e. eyelid, nose and lip) or large lesions on the ear, forehead or scalp. RT is often reserved for patients older than 60 years of age because of concerns about long-term sequelae if used in younger patients.[10] It is proposed to inform patients <60 years in age, especially organ transplant recipients, of the very low risk of radiation-induced, in-field malignancy in the future.[12]

Adjuvant treatment for high-risk cSCC

High-risk cSCC is by definition node-negative. Adjuvant (postoperative) RT at the primary tumour site is RT following resection of all macroscopic tumour with or without microscopic residual disease, and it is the only adjuvant therapy recommended for selected cases of high-risk cSCC in some guidelines. The rational for its use is the possibility to reduce the risk of local recurrence.

The European guidelines recommend postoperative RT after the surgical excision for cSCC with positive margins and in cases where re-excision is not possible.[8] The NCNN guidelines recommend multidisciplinary consultation and consider adjuvant RT for local, high-risk cSCC with negative margins, if extensive perineural, larger, or named nerve involvement, or if other high-risk features exist. It is noted, however, that 'the outcome benefit of adjuvant RT following resection of any cSCC with negative surgical margins is uncertain'.[10]

In BAD guidelines, it is recommended to offer adjuvant RT to people with incompletely excised cSCC, where further surgery is not possible and in those at high risk for local recurrence (PNI, i.e. multifocal, named nerve and/or diameter of nerve >0.1 mm, below the dermis, and immunosuppression or recurrent disease). Adjuvant RT may be recommended for completely excised T3 tumours, with multiple high-risk factors including >6 mm thickness and invasion beyond subcutaneous fat. It is recommended to not offer postoperative RT for patients with completely excised T1 or T2 cSCC and with microscopic, dermal only, nerve diameter <0.1 mm PNI.[12]

In the German guidelines, postoperative RD should be performed for R1 or R2 resection (if re-excision not feasible) and in the presence of the following risk factors: surgical margins <2mm and re-excision not feasible, extensive PNI.[13]

Guidelines on the management of advanced cSCC

A definition for locally advanced cSCC is given in the European guidelines; advanced cSCC is classified as locally advanced (lacSCC) and metastatic (mcSCC) including locoregional metastatic (in-transit and regional nodal metastasis) or distant metastatic cSCC, respectively. LacSCC is defined as non-metastatic cSCC, not amenable to either surgery or radiotherapy with reasonable hope for cure, because of multiple recurrences, large extension, bone erosion or invasion, or deep infiltration beyond subcutaneous tissue into muscle or along nerves, or else tumours in which curative resection would result in unacceptable complications, morbidity or deformity.[8] For staging and management of advanced cSCC, consultation in a multidisciplinary tumour board is necessary.

Surgical treatment for advanced cSCC

Regional therapeutic lymphadenectomy in patients with regional operable lymph node metastasis is associated with improved locoregional disease control.[13]

The BAD and AAD guidelines recommend to offer therapeutic regional lymphadenectomy for cSCC with regional lymph node metastases that are resectable.[11,12] The European, German and NCCN guidelines recommend therapeutic regional lymphadenectomy for cSCC with clinically or radiologically detected regional nodal metastasis.[9,10,13] Also, the German guidelines state that there are currently insufficient data regarding the value of regional lymphadenectomy following positive SLNB.[13] (Table 1). In addition, RT with or without concurrent systemic therapy may be indicated after regional lymph node dissection and are discussed below.

Primary definitive radiotherapy for advanced cSCC

In the European and German guidelines, RT should be performed in patients with inoperable disease.[9,13] In the NCCN guidelines, for patients with cSCC and inoperable nodal disease, multidisciplinary consultation should discuss RT with or without systemic therapy.[10] In the AAD guidelines, it is recommended to consider combination chemoradiation for inoperable disease with regional nodal metastasis.[11] The BAD guidelines recommend to consider regional lymphadenectomy or regional lymph node basin irradiation in selected people with cSCC for disease control even in the presence of distant metastases, especially in those undergoing multi-modality treatment.[12] (Table 1).

Systemic treatments for advanced cSCC

Systemic treatment options with a curative intent for advanced cSCC include immune checkpoint inhibitors, epidermal growth factor receptor (EGFR) inhibitors and chemotherapy/electrochemotherapy. A multidisciplinary decision approach is mandatory for all patients with advanced disease.[9]

The only approved systemic treatments for advanced cSCC are anti-programmed death receptor-1 (PD-1) agents, cemiplimab and pembrolizumab. Cemiplimab was approved by the US FDA in 2018 and by the European Medicines Agency (EMA) in Europe in 2019, for patients with metastatic cSCC or locally advanced cSCC who are not candidates for curative surgery or curative radiation. The approved regimen is a fixed dose of 350 mg every 3 weeks by IV infusion.[15] Efficacy has been shown in clinical trials reporting objective response of 50% for a cohort of patients with lacSCC or mcSCC in the phase 1 study and of 47% for mcSCC in the primary analysis of the pivotal phase 2 study (median follow-up: 11 months).[16] Rischin *et al.* reported long-term outcomes of the pivotal study in 59 patients with mcSCC, with objective response rate of 49.2% at a median follow-up pf 16.5 months. Importantly, the median duration of response was not reached, underscoring a sustained efficacy. A duration of response at 12 months was sustained by 88.9% of responders.[15] Immune-related adverse events (including maculpapular rash, hypothyroidism, diarrhoea and pneumonitis) occurred in around 60% and of grade 3 or higher in 13%.[15] Migden *et al.*[17] reported similar objective response rates of 44% for the group of patients with lacSCC in the pivotal trial. Pembrolizumab was approved by the FDA in 2020, for patients with recurrent or metastatic cSCC that is not curable by surgery or radiation. The approved regimen is a fixed dose of 200 mg every 3 weeks by IV infusion. In the pivotal phase 2 clinical trial in 105 patients with recurrent or metastatic cSCC, there was an objective response rate of 34.3%, while the median duration of response was not reached (median follow-up: 9.5 months).[18] Another phase 2 study evaluated pembrolizumab as first-line, systemic therapy for patients with unresectable cSCC and reported a higher objective response rate of 41% (median follow-up: 22.4 months).[19] Among contraindications, solid organ transplant recipients and patients with significant autoimmune disease or haematological malignancy were excluded from the clinical trials with anti-PD-1 agents for cSCC.

Platinum-based chemotherapy was used for advanced cSCC in the past. EGFR inhibitors have been reported for advanced cSCC, and most studies concern cetuximab, with considerable heterogeneity and small numbers of included patients. Cetuximab may be combined with chemotherapy or radiotherapy.[9,20] (Fig. 1).

The guideline recommendations for systemic treatment for advanced cSCC are presented in Table 1. The European guidelines recommend first-line systemic treatment with a PD-1 antibody for patients with mcSCC or lacSCC, who are not candidates for curative surgery or curative RT (with a strong recommendation). Chemotherapy can be used when patients fail to respond or are intolerant to anti-PD-1 immunotherapy. Platinum-based agents can be preferred. Chemotherapy may be more effective when used in combination with EGFRi or RT.[9] The NCCN guidelines give various recommendations for systemic therapy according to the extent of disease and whether systemic therapy will be used alone or with RT. Recommended systemic therapy options for use with RT, include (i) preferred regimens: cisplatin or clinical trial, (ii) other recommended regimens: none and (iii) useful in certain circumstances: EGFR inhibitors (e.g. cetuximab), or cisplatin + 5-FU, or carboplatin. Recommended options for systemic therapy alone include (i) preferred regimens: cemiplimab, pembrolizumab or clinical trial, (ii) other recommended regimens: carboplatin + paclitaxel and (iii) useful in certain circumstances: cetuximab, or capecitabine, or cisplatin, or cisplatin + 5-FU, or carboplatin.[10] The BAD guidelines recommend to consider immune checkpoint inhibitor treatment in patients with lacSCC where curative surgery or RT is not reasonable, or those with mcSCC, except OTRs or those who have significant autoimmune conditions (with a weak recommendation).[12] Chemotherapy and EGFRi are second-line treatments in the European and BAD guidelines, to consider in patients with mcSCC with contraindications to immune checkpoint inhibitors.[9,12] The German guidelines do not recommend

Table 1 Guidelines on the management of advanced cSCC

	European 2020[8,9]	US NCCN 2021[10]	US AAD 2018[11]	UK BAD 2020[12]	German 2020[13]
Surgery	Therapeutic regional lymphadenectomy for cSCC with clinically or radiologically detected regional nodal metastasis (GOR: B)	Therapeutic regional lymphadenectomy for cSCC with regional nodal metastasis (GOR: 2A)	Therapeutic regional lymphadenectomy for cSCC with regional nodal metastasis (GOR: B)	Therapeutic regional lymphadenectomy for cSCC with regional nodal metastasis (GOR: strong)	Therapeutic regional lymphadenectomy should be performed in clinically manifest LN metastasis (GOR: B)
Primary RT	RT should be performed in patients with inoperable disease (GOR: B)	Inoperable regional nodal metastasis should be treated with RT after multidisciplinary board (and consider concurrent systemic therapy after MDT) (GOR: 2A)	Consider combination chemoradiation for inoperable disease with regional lymph node metastasis (GOR: B)	Consider regional lymphadenectomy or regional lymph node basin irradiation in selected people with cSCC for disease control even in the presence of distant metastases, especially in those undergoing multi-modality treatment (GOR: GPP)	RT should be performed in patients with inoperable disease (GOR: B)
Systemic treatments	First-line treatment with a PD-1 antibody for patients with mcSCC or lacSCC who are not candidates for curative surgery or curative RT (GOR: A) (cemiplimab currently the only approved medication in Europe and USA, pembrolizumab approved in USA)	For lacSCC in non-surgical candidates, to consider for use in combination with RT, after MDT, preferred regimens: cisplatin or clinical trial (GOR: 2A)		Consider ICI in people with lacSCC where curative surgery or RT is not reasonable, or those with mcSCC, except OTR or those who have significant autoimmune conditions (GOR: Weak)	Systemic treatment should be reviewed in patients with recurrent local or locoregional disease if no surgical or RT options are available (GOR: expert consensus)
	Cetuximab may be used for patients with lacSCC and mcSCC, who have failed to respond or are intolerant to immunotherapy. Cetuximab combined with chemotherapy or RT is favoured over cetuximab monotherapy (GOR: C)	For lacSCC in which curative surgery and curative RT are not feasible, recommend MDT to consider systemic alone, preferred regimens: cemiplimab, pembrolizumab, or clinical trial (GOR: 2A)	EGFR inhibitors and cisplatin, as a single agent or in combination therapy may be considered for metastatic disease (GOR: B)	Consider chemotherapy or EGFR inhibitors† in people with mcSCC with contraindications to ICI (GOR: Weak)	No controlled or randomized studies on the benefit of systemic treatment for mcSCC. If used, systemic treatment should preferably be administered in the context of clinical trials (GOR: expert consensus)
	Chemotherapy can be used when patients fail to respond or are intolerant to anti-PD-1 immunotherapy. Platinum-based agents can be preferred. Chemotherapy may be more effective when used in combination with EGFRi or RT (GOR: C)	For new inoperable regional nodal metastasis, to consider concurrent systemic therapy with RT, after MDT. Options: cisplatin, clinical trial. Useful in certain cases: EGFRi, cisplatin + 5-FU, carboplatin (GOR: 2A)			

Table 1 *Continued*

European 2020[8,9]	US NCCN 2021[10]	US AAD 2018[11]	UK BAD 2020[12]	German 2020[13]
	For new inoperable or incompletely resected regional disease if curative RT not feasible, preferred options: cemiplimab, pembrolizumab, or clinical trial (GOR: 2A) If ineligible for ICI/clinical trial, to consider cisplatin, cisplatin + 5-FU, cetuximab, carboplatin			
	For regional recurrence or distant metastatic disease, MDT to consider systemic alone or with RT			

–, a recommendation is not mentioned; ADV, advanced; cSCC, cutaneous squamous cell carcinoma' ECE, extracapsular extension; EGFRi, EGFR inhibitors (e.g. cetuximab) GPP, good practice point; GOR, grade of recommendation; ICI, immune checkpoint inhibitors; lacSCC, locally advanced cSCC; LN, lymph node; mcSCC, metastatic cSCC; MDT, multidisciplinary tumour board meeting; MMS, Mohs micrographic surgery; OTR, organ transplant recipients; RT, radiotherapy; SLNB, sentinel lymph node biopsy; SSMDT, specialist skin cancer MDT.
†EGFR inhibitors are unlicensed for cSCC.

a specific systemic treatment for advanced cSCC. It is stated that systemic treatment should be reviewed in patients with recurrent local or locoregional disease if no surgical or RT options are available. Also, according to expert consensus, there are no controlled or randomized studies on the benefit of systemic treatment for metastatic cSCC, and if used, systemic treatment should preferably be administered in the context of clinical trials, while the decision to administer systemic treatment and its choice should be made by an interdisciplinary tumour board.[13]

Adjuvant treatment for advanced cSCC

The only adjuvant treatment recommended for advanced cSCC is postoperative RT after a therapeutic lymphadenectomy for cSCC with clinically apparent (via palpation or imaging) regional lymph node metastasis, depending on the number and size of nodal metastasis and the presence of extracapsular extension (ECE; Table 2).

In the European guidelines, adjuvant systemic therapy is not recommended for fully resected regional disease, except in the context of clinical trials.[9] In the NCCN guidelines, adjuvant systemic therapy is not recommended for most cases of fully resected regional disease, unless within a clinical trial. RT may be considered with or without systemic therapy for completely resected ECE or similar high-risk regional disease.[10]

Conclusions

There are various common recommendations across guidelines. Surgery with a curative intent is recommended as the treatment of choice for resectable high-risk or advanced (regional nodal metastatic) cSCC aiming to the complete removal of the tumour with uninvolved (negative) pathological margins. In case of involved (positive) histological margins, a re-excision is recommended if feasible in all guidelines. Definitive RT should be considered for non-surgical candidates. The only adjuvant treatment recommended for advanced cSCC is postoperative RT after a therapeutic lymphadenectomy for cSCC with clinically apparent (via palpation or imaging) regional lymph node metastasis. For immunosuppressed patients, it is recommended to consider modification or reduction in immunosuppression as appropriate. A multidisciplinary tumour board discussion is mandatory for all patients with advanced cSCC. The European guidelines recommend first-line systemic treatment with a PD-1 antibody for patients with mcSCC or lacSCC, who are not candidates for curative surgery or curative RT (in the absence of contraindications). Cemiplimab is the PD-1 antibody currently licensed in Europe for this indication. Also, the participation of patients in clinical trials should be encouraged.

The guidelines screen and grade a huge and quickly accumulating amount of evidence in order to provide physicians with evidence- and expert consensus-based guidance in clinical decisions. The recommendations across guidelines may converge,

Table 2 Guidelines on adjuvant treatment for advanced cSCC

	European 2020[8,9]	US NCCN 2021[10]	US AAD 2018[11]	UK BAD 2020[12]	German 2020[13]
Adjuvant RT	Adjuvant RT should be considered in cSCC of the head and neck with regional nodal metastases and ECE (GOR: B)	For cSCC of trunk and extremities, following therapeutic regional lymphadenectomy: -adjuvant RT may be considered especially if multiple involved nodes or ECE (GOR: 2A)	Surgical resection, with or without adjuvant RT (GOR: B) and possible systemic therapy recommended for regional lymph node metastasis (GOR: B)	Offer adjuvant RT following therapeutic regional lymphadenectomy for cSCC with high-risk pathology (e.g. two or more nodes, large nodes and ECE, UICC8 ≥pN1) (GOR: Strong)	Postoperative RT should be performed in: -R1 or R2 resection (if re-excision not feasible) -extensive lymph node involvement (>1 affected LN, LN metastasis >3 cm, capsular penetration) -intraparotid LN involvement (GOR: B)
		For cSCC of the head/neck, following therapeutic regional lymphadenectomy: -adjuvant RT depending on the number and size of metastatic nodes and ECE			There is currently insufficient data regarding the value of regional lymphadenectomy following positive SLNB
Adjuvant systemic therapy	Adjuvant systemic therapy is not recommended for fully resected regional disease. Ongoing clinical trials	Adjuvant systemic therapy is not recommended for most cases of fully resected regional disease, unless within a clinical trial (GOR: 2A)		–	–
		For completely resected ECE or similar high-risk regional disease, consider RT with or without systemic therapy in MDT (GOR: 2A)			

cSCC, cutaneous squamous cell carcinoma; RT, radiotherapy.

diverge or in some cases fail to provide any solid recommendation, underscoring current gaps in scientific knowledge.

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REVIEW ARTICLE

Treatment approaches of advanced cutaneous squamous cell carcinoma

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Abstract Common primary cutaneous squamous cell carcinoma (CSCC) accounts for 20% of keratinocyte cancers that is usually successfully treated with surgery or radiotherapy. In a minority of cases, CSCC lesions may progress to locally advanced or metastatic disease that may be difficult to be treated causing significant morbidity and mortality. Chemotherapies and targeted therapy with anti-epidermal growth factor receptor antibodies have been used off-label in small studies and case reports of advanced CSCC, but data are scarce and response short-lived. Recently, two PD-1 immune checkpoint inhibitors, cemiplimab and pembrolizumab, have been approved for the treatment of advanced CSCC; specifically the former can be administered in patients with locally advanced and metastatic tumours, while the latter in case of recurrent metastatic CSCC. The introduction of immune checkpoint inhibitors represents a breakthrough in the treatment of CSCC, since numerous clinical trials showed that these agents may provide remarkable clinical benefit with an acceptable safety profile, in a high-need population who had no standard of care. In addition, real-world studies are needed to validate the results observed in clinical trials and numerous clinical trials in the neoadjuvant or adjuvant setting are ongoing. Finally, further studies should investigate predictive biomarkers useful to better select patients to maximize the treatment efficacy.
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Definition and principles of treatment

The primary objectives of the treatment of cutaneous squamous cell carcinoma (CSCC) are the complete removal of the tumour with preservation of the maximal amount of normal surrounding tissue, achievement of a high cure rate and a good cosmetic outcome. The recent European interdisciplinary guidelines on invasive CSCC proposed to differentiate 'primary' CSCC, which includes common primary and locally advanced CSCC, from 'metastatic' CSCC.[1] Most patients with common primary CSCC, either low- or high risk, can be successfully treated with surgery, which represents the first-line treatment. Prospective studies showed that 4 mm safety excision margins in low-risk CSCC provide 95–97% cure rates. In high-risk CSCC, safety margins ≥10 mm are recommended depending on tumour- and patient-specific characteristics (e.g. cluster of lesions, coexisting medical conditions, histological subtype). Mohs micrographic surgery can be preferred in aggressive histological type, recurrent lesions and in facial CSCC, however, the need of special equipment and training, the length of the procedure and the high costs limit its wide use in many European countries.

Locally advanced CSCC (laCSCC) is a term used to define large, indurated and/or ulcerated, often painful plaques or nodules resulted from neglected lesions, multiple relapses and/or inappropriate management of common CSCC or biologically aggressive lesions that rapidly extend to the subcutaneous tissue (unresectable T3/T4 tumours) or involve bone and nerves.[2] LaCSCC may progress to lymph nodes and/or internal organs. The estimated incidence of locoregional or distant metastasis of CSCC varies from 1.2% to 13%: this wide range is likely due to differences in population samples, length of follow-up, and patients and lesions' characteristics.[1,3] LaCSCC and metastatic CSCC (mCSCC) are life-threatening diseases, associated with substantial morbidity, high impact on quality of life, and healthcare burden. Death may be caused by local invasion of vital structures or, less frequently, by metastatic spread.

The management of a patient with advanced CSCC should always be performed by a multidisciplinary team that includes professionals with experience on skin cancers (dermato-oncologists, dermato-surgeons, surgeons, radiologists, radiotherapists and pathologists). Decisions taken by the multidisciplinary team should be based on updated European and/or national guidelines, and provide the best innovative therapy or propose access to clinical trials available either in the centre or by referring patients to other centres and involve the patients and caregiver in the final treatment proposal.[4]

Surgical excision can be taken into consideration in some cases of laCSCC with no lymph node involvement, depending on lesion and patient characteristics. In contrast, destructive surgical approaches (cryotherapy, curettage and electrodesiccation, laser), photodynamic therapy and topical imiquimod or fluorouracil should never be considered in invasive CSCC.[2]

Radiotherapy may be an alternative treatment in patients who are not candidate to surgery because of multiple comorbidities, when curative surgery is not expected due to the aggressiveness of the tumour, when surgery may result in disfigurement (large lesions on the ear, eyelid) or in case of patients' refusal to underwent surgery.[2,3]

Systemic therapies

Until recently treatment of advanced CSCC represented a high unmet need since there were no approved systemic therapy and no standard of care.

Chemotherapy

Cytotoxic agents as cisplatin or carboplatin, 5-fluorouracil, bleomycin, methotrexate, Adriamycin, taxanes and gemcitabine have been used off-label in patients with advanced CSCC. Polychemotherapy seems to be more effective than monochemotherapy, however, data are scarce and inconsistent, responses are short-lived and associated with high toxicity.[2,3,5] According to the recent European consensus and BAD guidelines, systemic chemotherapy can be used only in patients who fail to respond or are intolerant to anti-PD-1 immunotherapy.[2,6]

Targeted therapies – EGFR inhibitors

Among EGFR inhibitors, only cetuximab is approved for the treatment of head and neck SCC but not for CSCC. In a phase II trial including 36 patients with unresectable CSCC, cetuximab (initial dose: 400 mg/m^2 followed by weekly doses of 250 mg/m^2, for at least 6 weeks) provided a disease control rate of 69% at 6 weeks, with an objective response rate (ORR) of 28% and a stable disease of 41.7%. The mean overall survival (OS) was 8.1 month and the median progression-free survival (PFS) was 4.1 months.[7] Most adverse events occurring during treatment with EGFR inhibitors affect the skin, are dose-dependent, have an early onset and involve aesthetically sensitive areas (face and upper trunk) resulting in a great impact on patient's quality of life.[5] In additional retrospective and prospective non-randomized studies, a small number of patients with laCSCC and mCSCC have been treated with cetuximab and no robust conclusions can be drawn. Similar to the suggestions provided for chemotherapy, the current International guidelines recommend to use cetuximab in patients who have failed to respond or have contraindication to immune checkpoint inhibitors.[2,6]

Immunotherapy: immune checkpoint inhibitors

Immune checkpoint inhibitors have represented a major breakthrough for the treatment of advanced CSCC, addressing a large unmet need. Cemiplimab, a humanized IgG4 PD-1 blocker, binds to the extracellular domain of the PD-1 receptor limiting the interaction of PD-1 with its ligands (PD-L1 and PD-L2), thus restoring the activation of the T cells and the anti-tumour response. Cemiplimab has been approved by FDA (September 2018) and EMA (July 2019) at the dosage of 350mg intravenously (i.v.) every 3 weeks, for the treatment of adult patients with laCSCC or mCSCC who are not candidates for curative surgery or radiotherapy. The rationale for the use of PD-1 inhibitors in CSCC is based on the high frequency of somatic mutations (i.e. high mutational burden) in CSCC due to chronic sun exposure that are more likely to provide a clinical response to PD-1 blockade possibly through the generation and expression of neoantigens that activate T cells. The initial study of Migden *et al.*[8] reported the results of the expansion cohorts of the phase I study (16 patients with laCSCC and 10 with mCSCC) and of the pivotal phase 2 study of a metastatic-disease cohort (59 patients). In both studies, the patients received i.v. cemiplimab 3 mg/kg every 2 weeks for a maximum of 48 weeks in the phase I study and 96 weeks in the phase II study. All patients had been extensively pretreated with surgery, systemic therapies or radiotherapy. Objective response (OR) to cemiplimab was achieved in 13/26 (50%) patients of the expansion cohorts of the phase I trial, and in 28/59 (47%) patients of the phase II metastatic cohort. Among patients who obtained a response, 57% had a response duration longer than 6 months. The safety profile was good: most adverse events consisted of grade 1–2 fatigue, diarrhoea, nausea, constipation and rash. Treatment discontinuation occurred in 8% and 7% of the patients in the phase I and phase 2 cohorts, respectively.[8] A subsequent open-label, phase II, single-arm trial showed an OR to cemiplimab (3 mg/kg i.v. every 2 weeks for up to 96 weeks) in 34 of 78 (44%) patients with laCSCC. The best overall response included 10 patients (13%) with complete response and 24 (31%) with partial response. The median time to response was 1.9 months and duration of response (DOR) ≥6 months was osbserved in 23 (62.8%) patients. Remarkably, the median DOR had not been reached at data cut-off with a longest DOR at data cut-off of 24.2 months.[9] An example of the successful clinical results of cemiplimab in one of our patients is illustrated in Fig. 1. An additional phase 2 study evaluated efficacy and safety of

cemiplimab in two groups of patients: (i) group 1 that included 59 patients with mCSCC from the pivotal study who received 3 mg/kg i.v. every 2 weeks and (ii) group 3 including 56 patients with mCSCC who received 350 mg i.v. cemiplimab every 3 weeks. The ORR was 49.2% in group 1, 41.1% in group 3 and 45.2 in both groups combined. DOR at 8 months was 95.0% (95% CI, 69.5–99.3%) in patients of the group 3 and 88.9% (95% CI, 69.3–96.3%) at 12 months in group 1 patients. This study showed that cemiplimab provided a durable response and further confirmed the acceptable safety profile.[10] Notably, the fixed dose of 350 mg every 3 weeks, now approved by the FDA and EMA, has demonstrated similar pharmacokinetics to dosing based on weight.

A recent systematic review showed that in an indirect treatment comparison with other systemic mono-chemotherapies, cemiplimab provided higher PFS and OS.[11] A post hoc exploratory analysis of a phase 2 clinical trial reported a meaningful reduction in pain was observed already at the 3rd cycle of cemiplimab treatment with improvement in global health status and health-related quality of life.[12]

Since elderly and immunosuppressed patients are often significantly underrepresented in clinical trials, Glenn *et al.*[13] presented real-life data from a cohort of 61 patients with advanced CSCC treated with cemiplimab over 5 years. A lower percentage of ORRs was observed compared to those observed in clinical trials (31.5 vs. 48%, $P < 0.01$), with a higher number of progressive disease events (59 vs. 16.5%, $P < 0.01$). Grade 3-4 immune-related adverse events were overall in line with previous studies (20% vs. 29–42%), and more common among responders being gastrointestinal or hepatic toxicity the most frequent.[13]

Other immune checkpoint inhibitors have been recently investigated in patients with advanced CSCC. In a single-arm phase 2 study, pembrolizumab (200 mg every 3 weeks) was administered in patients with recurrent or mcSCC.[14] After a median follow-up of 11.4 months, the ORR was 34.3%, with complete response in four patients (3.8%) and partial response in 32 patients (30.5%). Disease control rate was 52.4%. Efficacy was comparable in locoregional-only and distant mCSCC subgroups. The safety profile consisted of treatment-related adverse events in 66.7% of patients, being pruritus (14.3%), asthenia (13.3%) and fatigue (12.4%) the most common. Grade 3–5 adverse events occurred in 5.7% of patients.[14] The efficacy and safety of pembrolizumab (200 mg i.v. every 3 weeks) was also assessed as first-line monotherapy in patients with laCSCC or mCSCC, showing ORR in 41% of patients at week 15, durable clinical responses and manageable safety.[15] Pembrolizumab at the dosage of 200 mg i.v. every 3 weeks or 400 mg i.v. every 6 weeks was approved by FDA in June 2020 for patients with

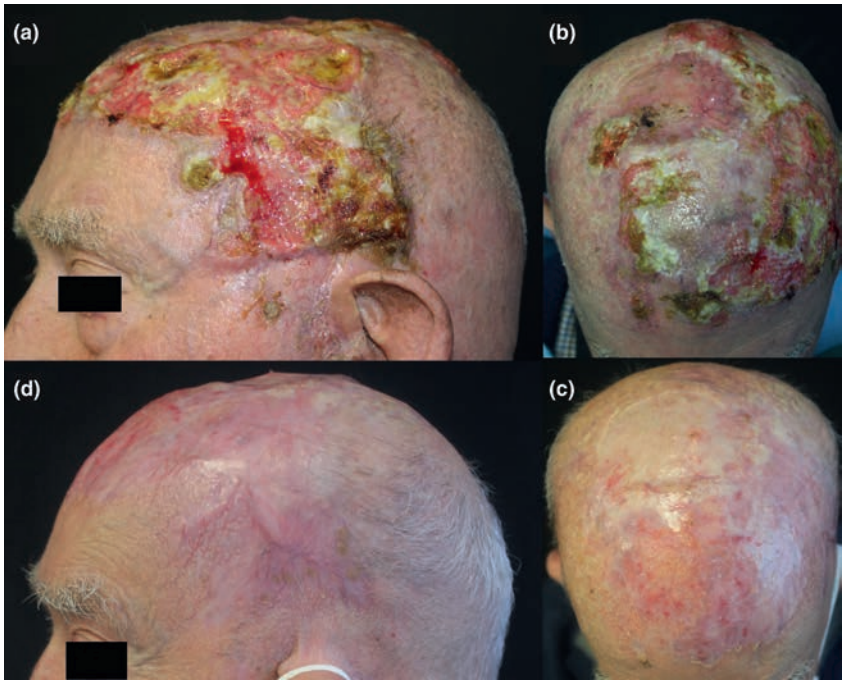

Figure 1 A 92-year-old man with a locally advanced CSCC previously treated with surgery and radiotherapy. Clinical images of a ulcerated plaque located on the left temporal region (a) and scalp (b) before and after treatment with cemiplimab 350 mg i.v. every 3 weeks for 12 months (c, d). The patient is still under treatment with cemiplimab and did not present any drug-related adverse event.

recurrent or metastatic CSCC that is not curable by surgery or radiation.

Conclusions

Treatment with immune checkpoint inhibitors has profoundly changed the therapeutic management of advanced CSCC. Cemiplimab and pembrolizumab are two anti-PD1 agents approved by FDA (while pembrolizumab is not yet approved by EMA), for the treatment of advanced CSCC that showed remarkable clinical benefit and durable responses along with an acceptable safety profile. Currently, immune checkpoint inhibitors represent the standard of care in both laCSCC and mCSCC. Real-life studies are needed to validate the effectiveness and safety of anti-PD1 immunotherapy in both laCSCC and mCSCC. In addition, numerous clinical trials are currently ongoing to treat advanced CSCC with the use of cemiplimab intralesionally or in the neoadjuvant or adjuvant setting (following surgery and radiation) as well as studies on pembrolizumab.[16]

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REVIEW ARTICLE

Management of immune-related adverse events in anti-PD-1-treated patients with advanced cutaneous squamous cell carcinoma

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Abstract Immune checkpoint inhibitors (ICI) have shown very promising results in the management of patients with inoperable or metastatic cutaneous squamous cell carcinoma (cSCC). However, ICI can cause a range of immune-related adverse events (irAEs) affecting a multitude of organs including skin, gastrointestinal tract, endocrine system, heart, lung, kidneys and the nervous system. In principle, clinical management irAEs does not change significantly with respect to the kind of cancer treated with ICI. However, advanced cSCC typically occurs in a clinically challenging patient population typically presenting with advanced age and/or significant comorbidities such as immunosuppression due to haematological malignancies and their respective treatment. Moreover, many patients with advanced cSCC are organ transplant patients taking immunosuppressants. As a consequence use of ICI *per se* and management of ICI-induced irAEs generates more complexity and difficulties in patients with cSCC compared to other entities. Here, we provide a brief review on the management of anti-programmed cell death protein 1-induced irAEs in patients with cSCC focusing on the characteristic clinical challenges present in this population.
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Conflicts of interest

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Introduction

Immune checkpoint inhibitors (ICI) have provided very promising results in the management of patients with inoperable or metastatic cutaneous squamous cell carcinoma (cSCC).[1–5] In contrast to other cancer therapies such as chemotherapy, however, ICI can produce a wide range of immune-related adverse events (irAEs) affecting a multitude of organs such as skin, gastrointestinal tract, endocrine system, heart, lung, kidneys and the nervous system (Table 1). irAEs may develop at any time as indicated by a wide range of first occurrence for different organs (e.g. from few days after initiation up to 15 months for skin or up to 12 months for the gastrointestinal tract). The anti-programmed cell death protein 1 (PD-1) antibody cemiplimab has recently been approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency for the treatment of patients cSCC.[2] Moreover, pembrolizumab – another anti-PD-1 antibody – has been approved by the FDA.[3] In clinical trials, other anti-PD-1 and PD-L1 antibodies, including nivolumab, atezolizumab and avelumab, are actively investigated in cSCC patients.[1–12]

Peculiarities of cSCC patients with anti-PD-1 therapy

In principle, the management of irAEs is comparable between different entities treated with ICIs. Similar to patients with Merkel cell carcinoma, however, patients with advanced cSCC represent a clinically challenging population due to several specific characteristics.[13–15] Most frequently, cSCC patients belong to the elderly and suffer from comorbidities which complicate not only use of ICI, but also management of ICI-induced irAEs (Table 2).

Table 1 Characteristics of patients with cutaneous squamous cell carcinoma with regard to the use of immune checkpoint inhibitors and treatment of immune-related adverse events

- Advanced age
- Many co-morbidities and medications
- Haematological co-malignancies
- Often organ transplant patients
- High-risk population for severe COVID-19
- Mental health issues
- Reduced compliance/adherence

Table 2 Collection of immune-related adverse events (irAE) in cancer patients treated with immune checkpoint inhibitors

Organ system	irAE
Cardiovascular	Myocarditis, pericarditis, vasculitis, thromboembolic events
Cutaneous	Pruritus, macular-papular rashes, lichenoid dermatitis, vitiligo, severe cutaneous reactions
Endocrinological	Hypo/hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes
Gastrointestinal	Colitis, hepatitis, pancreatitis
Haematological	Autoimmune haematolytic anaemia, aplastic anaemia, neutropenia, haemophagocytotic lymphohistiocytosis
Musculoskeletal	Myositis, inflammatory arthritis, polymyalgia rheumatica
Neurological	Myasthenia gravis, Guillain-Barré syndrome, peripheral and autonomic neuropathy, encephalitis, aseptic meningitis
Ocular	Uveitis, iritis, episcleritis, opticus neuritis
Pulmonary	Pneumonitis, sarcoid reactions
Renal	Nephritis

For example, medication for the treatment of various comorbidities, such as different cardiovascular, neurological and metabolic conditions, may render employment of ICI in this population more complex and difficult. Cognitive and sensory health issues including dementia, seeing and hearing impairment, and reduced compliance, therapy adherence, and capability to understand properly treatment schedules, further complicate both use of ICI and management of irAEs. Using age and performance status to assess prognosis is likely insufficient. Instead, a comprehensive geriatric assessment of functional, mental and nutritional factors may be necessary to guide the management of ICI treatment in such a patient population.[16,17]

The current COVID-19 pandemic renders the use of ICI more difficult as well, particularly in the elderly population discussed above. Indeed, over the course of ICI treatment, supportive immunosuppressive therapies may be required to treat therapy-associated irAEs, which in turn may increase the risk of infection with SARS-CoV-2 depending on the immunosuppressive agents used.[18,19] However, immunosuppressive intervention in COVID-19 patients with a severe course of disease may actually be employed to temper an over-reactive immune response, exemplified by a condition termed 'cytokine storm'. In this context, it would be preferable to use corticosteroids, TNF-α-blockers and IL-6-blockers over other immunosuppressive agents that may cause severe lymphopenia. Nonetheless, patients receiving immunosuppressants for treatment of ICI-induced irAEs should be placed under particularly close surveillance for the occurrence of symptoms or signs suggestive of SARS-CoV-19 infection or worsening of pre-existing COVID-19. Importantly, there is no convincing evidence that ICI are generally immunosuppressive.[18] Therefore, avoiding the employment of ICIs to minimize the risk of SARS-CoV-2 infection altogether will not provide any benefit to these patients, but would deprive them from a highly effective treatment option.

In contrast to other patient populations such as melanoma patients, individuals with cSCC typically present with a higher number of significant co-morbidities, including haematological malignancies.[5] The high prevalence and fatality of cSCC in patients with concomitant haematological neoplasms have been mainly attributed to an impaired immune function, which is particularly true for patients with chronic lymphatic leukaemia.[5] In patients with polycythaemia vera or myelodysplastic syndromes, however, immunosuppressive effects rather result from treatment than from the haematological malignancy itself. Cytoreductive agents, for example, might contribute to the immunocompromised state in these patients. In this context, it was shown that treatment outcome by ICI was significantly reduced in cSCC patients with haematological malignancies regarding progression-free survival compared to those without. By contrast, this was not the case for melanoma and Merkel cell carcinoma patients. Unfortunately, this particular patient population, for example, cSCC patients with haematological malignancies, is usually excluded from clinical trials.[1,5] Hence, management of treatment safety in this population mainly depends on real-life clinical experience. The same is true for organ transplant patients who develop cutaneous neoplasms such as cSCC with an aggressive course of disease very frequently.[15] The use of ICI in these patients is complicated by two major issues. On the one hand, there is a high risk of transplant rejection under ICI. On the other hand, concomitant immunosuppressive medications counteract anti-tumour directed immune activation by ICI. Finally, patients treated with immunosuppressive drugs who additionally may receive a host of other potentially toxic drugs may generally experience more severe side effects. In such a complex therapeutic setting, it may be impossible to decide which adverse event can definitively be ascribed to a single drug. Taken together, the above described therapy situations highlight potential issues and challenges in the management of cSCC patients using anti-PD-1 antibodies.

Anti-PD-1-induced irAEs and their management

The safety of the anti-PD-1 antibody cemiplimab monotherapy was studied in two clinical trials (R2810-ONC-1423, R2810-

ONC-1540) for 591 patients with advanced solid malignancies, including 219 patients with cSCC. irAEs, including grade 5 (0.7%), grade 4 (1.2%), and grade 3 (6.1%), were observed in 20.1% of patients treated with cemiplimab in clinical trials. In 4.4% of patients, the occurrence of irAEs resulted in permanent cessation of immunotherapy. The most frequent irAEs induced by cemiplimab therapy were hypo- or hyperthyroidism, pneumonitis, cutaneous reactions including severe conditions (Stevens–Johnson syndrome, toxic epidermal necrolysis etc.), and hepatitis. In general, oral and intravenous corticosteroids are the mainstay of irAEs management. Depending on the irAEs, their severity and non-responsiveness to corticosteroids, other immunomodulatory and immunosuppressive drugs may be indicated, including infliximab, vedolizumab, cyclosporine, mycophenolate mofetil, and intravenous immunoglobulins. Moreover, a close collaboration with respective specialists, including endocrinologists, neurologists and ophthalmologists, is strongly recommended for managing irAEs.[7–9,11,12] In the following paragraphs, the clinical management of specific irAEs is discussed in more detail.

Cardiovascular irAEs

Cardiovascular irAEs can occur at any time under ICI therapy and may present as myocarditis, pericarditis, arrhythmia, pericarditis, pericardial effusions, impaired ventricular function with heart failure and vasculitis. Possible symptoms include chest pain, arrhythmia, palpitations, peripheral oedema, progressive or acute dyspnoea, pleural effusion and fatigue. In mild cases, ICI should be withheld. If there is no immediate improvement of symptoms after administration of corticosteroids, initiation of mycophenolate, administration of infliximab or antithymocyte globulin is recommended. In the event of non-life-threatening venous thromboembolism under anti-PD-1 blockers, which may manifest by swelling of extremities, pain, redness, cyanosis, dyspnoea, chest pain, cough, haemoptysis and fever, the continuation of ICI therapy and guideline-based anticoagulation is recommended. For life-threatening disease courses with haemodynamic and/or neurologic instability, ICI therapy should be discontinued.[7–11]

Cutaneous irAEs

Cutaneous irAEs occur in about half of patients and are usually observed within the first few cycles of ICI therapy.[20] Apart from unspecific symptoms such as itching and a burning sensation, more specific conditions are observed, including erythematous macular-papular (Fig. 1) or lichenoid rashes, alopecia, stomatitis, vitiligo (Fig. 2), lightening of naevi, sarcoid reactions, vasculitis and bullous dermatoses. The latter may include bullous pemphigoid and more severe skin reactions such as Stevens–Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms. In severe cases, prompt hospital admission and emergency dermatology consultation are needed, since these conditions may become fatal if not diagnosed in a timely manner and treated appropriately with high-dose glucocorticoids.[7–9,11,12,20]

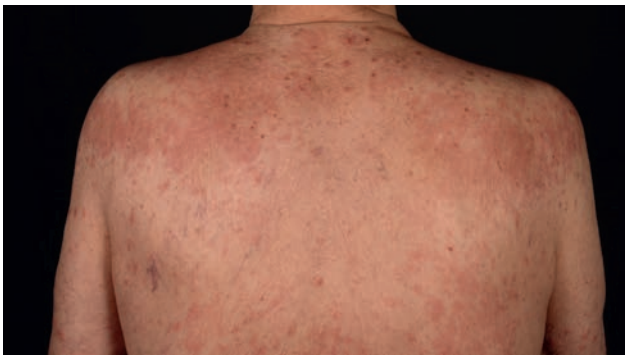

Figure 1 Showing an 81-year-old man with metastatic non-small cell lung cancer who developed a generalized itchy macular-papular rash under anti-PD-1 treatment.

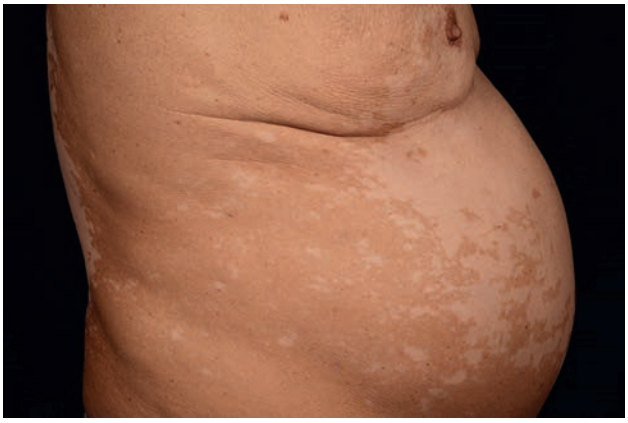

Figure 2 Showing a 62-year-old man with metastatic melanoma who developed widespread vitiligo under anti-PD-1 treatment.

Endocrinological irARs

Thyroid dysfunction like hypo- or hyperthyroidism and thyroiditis are among the most common early side effects of patients receiving ICI. The incidence of thyroid dysfunction in patients treated with anti-PD-1 or anti-PD-L1 ranges from 4% to 20%. Hyperthyroidism, for example, occurs in about 2% of patients receiving cemiplimab. By contrast, hypothyroidism occurs in 7%. Usually, it is possible to continue ICI, long-term discontinuation is required in <1% of patients. In patients who report onset of fatigue, weight gain, hair loss, cold intolerance, constipation, depression, hypothyroidism should be suspected. By contrast, symptoms like atrial fibrillation, diarrhoea, heat intolerance, excessive diaphoresis and weight loss can point to

hyperthyroidism. Thyrotoxicosis may require the use of corticosteroids which appears to reduce the required dose of hormone-replacement therapy with levothyroxine during the following hypothyroid phase. Unlike ICI agents such as ipilimumab, anti-PD-1 monotherapy with cemiplimab or pembrolizumab has been only rarely associated with hypophysitis, a condition with the potential to cause an adrenal crisis. Non-specific symptom such as headaches and fatigue are predominantly observed in ICI-induced hypophysitis, hyponatraemia is present in half of patients. A diagnosis is made by brain/sella magnetic resonance imaging. Acute morbidity and mortality from hypophysitis are mainly due to central adrenal insufficiency. High-dose corticosteroids, substitution of electrolytes and physiologic replacement doses of corticosteroids are usually required to manage hypophysitis. Patients with ICI-induced type 1 diabetes mellitus (T1DM) may initially present with diabetic ketoacidosis. ICI-induced T1DM occurs more frequently in middle-age and elderly adults. Although ICI-induced T1DM with subsequent diabetic ketoacidosis represents a rare irAE, it is potentially fatal and requires prompt diagnosis and treatment. Diabetic ketoacidosis must be treated in a timely manner with intravenous insulin infusion, intravenous fluid and electrolytes. Consultation by an endocrinologist is recommended in case of severe endocrinological irARs.[7–11]

Gastrointestinal irAEs

Gastrointestinal irAEs include colitis/enteritis, hepatitis and pancreatitis. Severe colitis occurs in almost 10% of patients treated with ICI overall, with anti-PD-1 antibodies causing colitis less frequently than other ICIs. Symptoms typically occur within the first few weeks of initiating ICI initiation. The mainstay of treatment is administration of systemic corticosteroids. In severe cases refractory to mono-therapy with corticosteroids, immunosuppressants such as cyclosporine and mycophenolate mofetil, or infliximab and vedolizumab may be considered. ICI-induced hepatitis is primarily detected serologically through elevation of liver enzymes, with or without a concomitant increase in serum levels of bilirubin. Hepatitis occurs in up to 10% of patients treated with ICI. Most cases are not severe and resolve with transitory discontinuation of ICI. Nevertheless, in rare cases, severe hepatic failure may occur. If ICI-induced hepatitis/transaminitis does not improve within a week of corticosteroid therapy, other immunosuppressive agents, including mycophenolate mofetil, should be considered. IrAEs affecting the exocrine pancreas are less common and usually present as a transient increase in lipase and/or amylase serum levels. Acute onset of symptomatic pancreatitis is a rare event. In the absence of clinical symptoms, it is usually not necessary to treat aberrant serum levels of pancreatic enzymes with corticosteroids. However, for symptomatic patients or patients with very high lipase and/or amylase levels, systemic therapy with corticosteroids is indicated.[7–11]

Hematological irAEs

Aplastic anaemia, haemolytic anaemia, neutropenia and autoimmune thrombocytopenia are reported rarely as irAEs of ICI, but nonetheless need to be taken seriously for their potential to take on life-threatening clinical courses. Apart from systemic corticosteroids, treatment of these irAEs may include transfusion support, management of neutropenic fever and of acute bleeding complications related to severe thrombocytopenia, respectively. In severe cases, immediate treatment with intravenous immunoglobulins in combination with corticosteroids may be required. In a meta-analysis comprising 9324 patients treated with ICI, the frequency of neutropenia as an irAE was <1%.[18] Similarly, lymphopenia rather represented a general hallmark of elderly patients with metastatic cancer, rather than resulting from treatment with ICI. However, cytopenia in the absence of previous cytotoxic chemotherapy could also indicate development of haemophagocytic lymphohistiocytosis (HLH), a severe, potentially fatal condition that is characterized by T lymphocyte overactivation and consecutive organ damage. Morbidity and mortality due to HLH are predominantly due to delayed diagnosis, and a high index of suspicion would serve to facilitate early intervention with high-dose corticosteroids or, in severe cases, with etoposide or tocilizumab.[7–9,11,12]

Musculoskeletal irAEs

Musculoskeletal symptoms are relatively common and occur in about 40% of ICI-treated patients. The most common rheumatological irAEs are polymyalgia-like syndromes, arthritis and myositis. These present clinically with relatively unspecific symptoms that generally occur in the elderly with high frequency, and include joint pain and stiffness in the proximal upper and/or lower extremities, difficulty with active movement, muscle weakness and joint swelling. For mild forms of musculoskeletal irAEs, primary analgesia should be performed using non-steroidal antiphlogistic drugs. If symptoms are not under control, systemic or intra-articular application of corticosteroids may be used. In case of severe irAEs with risk for long-term damage, immunosuppressive therapy is recommended, including methotrexate, azathioprine, mycophenolate mofetil, rituximab, tocilizumab and, if necessary, discontinuation of ICI therapy.[7–11]

Neurological irAEs

Immune checkpoint inhibitors-associated neurological irAEs, such as myasthenia gravis, Guillain-Barré syndrome, peripheral neuropathy, autonomic neuropathy, transverse myelitis, or aseptic meningitis, and encephalitis, are rare and reported in <5% of patients treated with ICI. The most documented symptoms are peripheral sensory neuropathy and headache. Current data suggest that a severe course of neurological irAEs is observed in about 1% of patients. In addition to therapy with high-dose corticosteroids, administration of intravenous immunoglobulins and/or plasmapheresis may be recommended in severe cases.

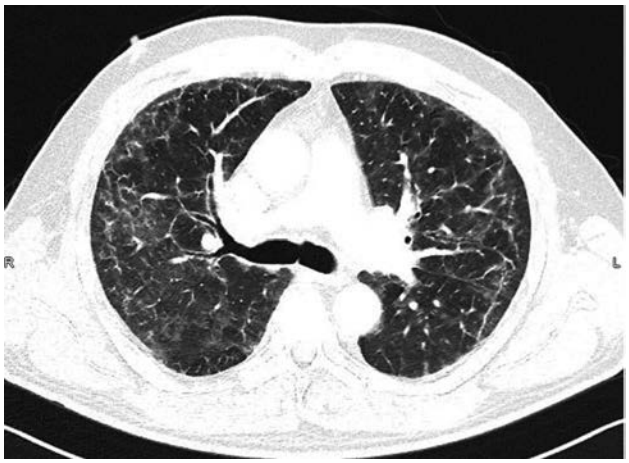

Figure 3 Chest computed tomography of a melanoma patient receiving precision immunotherapy with ipilimumab and nivolumab. Pneumonitis with diffuse alveolar damage is observed including reticular markings, traction bronchiectasis and ground-glass opacities.

Discontinuation of ICI therapy is indicated in cases of life-threatening or persistent serious irAEs.[7–11]

Ocular irAEs

Although rare (<1% of patients), ocular irAEs may also present as severe side effects, leading to reduced quality of life and eventually discontinuation of ICI. Ocular irAEs most frequently occur during the first months of ICI treatment and may present with symptoms such as scotomas, alterations of colour vision, blurred/double vision, visual field changes, tenderness and pain with eye movement. Ocular irAEs include blepharitis, uveitis, iritis, episcleritis, ulcerative keratitis and neuritis of the optic nerve. Many ophthalmological irAEs may be managed with topical, intra- or peri-ocular corticosteroids. In severe cases, systemic corticosteroids and immunosuppressive agents must be used.[7–9,11,12]

Pulmonary irAEs

Pneumonitis is a well-described side effect in patients taking anti-PD-1 agents that usually presents as interstitial lung disease (Fig. 3). However, the radiological features of ICI-induced pneumonitis are quite unspecific and can be confused with changes seen in viral pneumonia such as COVID-19 or sarcoid-like reactions.[18] One-third of pneumonitis cases represent incidental findings by radiological imaging during staging exams. For example, ICI-induced pneumonitis occurs in about 4% of patients receiving cemiplimab.[2] However, although occurring relatively rarely as an irAE overall, pneumonitis is one of the most common causes of ICI-related death. In addition to pneumonitis, ICI-treatment can be associated with pleural effusions, pulmonary sarcoidosis and sarcoid reactions. With respect to clinical management, patients with symptoms such as dyspnoea, cough, fever and chest pain should discontinue anti-PD-1 blockers at least temporarily. Patients with irAEs grade 2 or higher must be treated with systemic corticosteroids for 4–6 weeks. An escalation of immunosuppressive treatment with infliximab and/or cyclophosphamide must be considered in corticosteroid-refractory pneumonitis.[7–11]

Renal irAEs

Nephrological adverse events during ICI therapy, such as nephritis (symptomatic or asymptomatic), belong to the relatively rare irAEs occurring in 1–2% of patients, which usually manifest in increasing renal retention parameters, changes in urine colour or volume, oedema/anasarca, or haematuria. In addition to high-dose corticosteroid therapy, immunosuppressive therapy with, for example, mycophenolate may be considered in severe cases.[7–11]

Conclusion

Patients with advanced cSCC are characterized by high age, history of organ transplantation, immunosuppression and significant comorbidities including multiple medications. Hence, there exist potential issues and challenges in the management of cSCC patients using anti-PD-1 antibodies. In particular, the management of irAEs in patients with advanced cSCC may be more complicated than in cancer populations of younger age, less comorbidities etc. Nonetheless, the high efficacy of anti-PD-1 agents far outweigh the challenges potentially arising in patients with advanced cSCC.

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The patients in this manuscript have given written informed consent to the publication of their case details.

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REVIEW ARTICLE

Management of partial and non-responding cutaneous squamous cell carcinoma

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Abstract Cutaneous squamous cell carcinoma (cSCC) and basal cell carcinoma are the most common types of skin cancer. For patients with locally advanced and metastatic cSCC, the programmed cell death 1 (PD-1) inhibitor cemiplimab is approved for systemic treatment. Despite this revolutionary immunomodulatory therapeutic approach, tumours may fail to respond either completely or partially. In addition to the previously established local treatment with radiotherapy or systemic treatment with chemotherapy and epidermal growth factor receptor inhibitors, ongoing trials are currently focussed on re-stimulating the antitumour immune response in patients with advanced cSCC refractory to PD-1 inhibitors. In this review, ongoing and recently finished trials with different therapeutic approaches will be discussed.
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Conflict of interest

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Introduction

The majority of cutaneous squamous cell carcinoma (cSCC) can be cured by complete surgical excision of the primary tumour. According to different guidelines, local radiotherapy is recommended for patients whose cSCC cannot be excised completely ('locally advanced', lacSCC). For patients with metastatic cSCC (mcSCC), platinum-based chemotherapy has long been the recommended systemic therapy.[1] There are few

heterogeneous and often small case series with partly unknown response criteria demonstrating overall response rates (ORR) varying from 14%–86% with a duration of responses (DOR) between 5–11.8 months. Patients often suffer from severe toxicity.[2] The discovery of molecular pathways inducing the development of cSCC and the elucidation of 'cancer cell—immune cell—interactions' revealed additional therapeutic approaches for lacSCC and mcSCC (advanced cSCC). Due to the elevated mutational burden in cSCC and the positive correlation between mutational burden and response rate to inhibitors of programmed cell death 1 (PD-1), immune checkpoint inhibitors (ICI) directed against PD-1 were considered promising candidates.[3] Inhibition of PD-1 prevents tumour-induced immunosuppressive modulation of T cells, leading to the restoration of the antitumour immune cell response.[4] In 2014, the first approval of PD-1 inhibitor therapy was given for malignant melanoma. Despite the revolutionary therapeutic approach, clinical studies revealed lack of response in 40%–45% of patients treated with PD-1 inhibitors.[5] Furthermore, long-lasting tumour control (over 5 years) was only achieved in roughly 1/3 of patients treated in first-line. For patients with advanced cSCCs, the PD-1 inhibitor cemiplimab was approved by the US Food and Drug Administration (FDA) in 2018 and by the European Medicines Agency in 2019.[1] In 2020, the PD-1 inhibitor pembrolizumab was approved by the FDA as well.[6] In a phase I study for patients with advanced cSCC, response rate to cemiplimab was 50% under therapy with 3 mg/kg every second week (Q2W).[7] In the phase II study with the same dose scheme, ORR was 49.2% with a durable disease control rate (DDCR, the proportion of patients without progressive disease for at least 105 days as defined in the clinical protocol) of 61%. In the phase II study for application of cemiplimab 350 mg Q3W, ORR was 41.1% with a DDCR of 57.1%.[8] In another phase II study, objective response was observed in 34 of 78 patients suffering from lacSCC and receiving cemiplimab 3 mg/kg Q2W.[9] For those patients with partial and missing response, there are currently no approved therapeutic alternatives. Clinical trials focus on re-stimulating the immune system and enhancing tumour immunogenicity for an antitumour immune response. In this review, ongoing and recently finished trials with potential therapeutic approaches for patients with advanced cSCC will be discussed regarding experience from other PD-1 inhibitor refractory cutaneous malignancies (Table 1).

EGFR inhibitors

An elevated expression of the epidermal growth factor receptor (EGFR) was found in both mcSCC and primary cSCCs with poor clinical outcome.[10] The stimulation of EGFR as part of the receptor tyrosine kinase family activates multiple pathways affecting cellular proliferation and resistance to apoptosis. Molecular therapies targeting EGFR have been shown to decrease signal transduction of the EGFR pathway. EGFR inhibitors as well as their combined use with radiotherapy and chemotherapy for the treatment of cSCC have been described in multiple reviews.[2,11] However, targeting EGFR led to ORR between 10%–31% with DOR between 4.7–8 months in different clinical studies while frequently inducing pruritus, acne-like rash and/or desquamation.[2] The application of EGFR therapy is expected to remodel the tumour environment favouring response to PD-1 inhibitor therapy.[12] The recently initiated phase II trial AliCe includes patients with advanced cSCC refractory to PD-1 inhibitor therapy. Patients receive the EGFR inhibitor cetuximab and the PD-L1 inhibitor avelumab (EudraCT 2018-001708-12, results pending). Additionally, patients with advanced cSCC and prior anticancer treatment can be included in an ongoing phase I trial for treatment with cetuximab and the tyrosine kinase inhibitor lenvatinib (NCT03524326). An interim analysis which also included therapy-naïve patients with head and neck SCC showed an ORR of 67% (n = 6/9 evaluable patients).[13] Further results on the treatment of advanced cSCC refractory to PD-1 inhibitor therapy with lenvatinib are pending, but an interim analysis on the combined use of lenvatinib and pembrolizumab in melanoma patients who had previously failed to respond to PD-1 inhibitor or other systemic therapy (n = 103) showed an ORR of 21.4% [two complete responses (CR), 20 partial responses (PR); NCT03776136].[14]

Toll-like receptor agonists

Toll-like receptors (TLR) are a class of pattern recognition receptors with TLR9 being predominantly located intracellularly in immune cells, including dendritic cells, macrophages, natural killer cells and other antigen-presenting cells. Thus, TLR 9 agonists, like tilsotolimod, both stimulate those immune cells and induce interferon-α expression resulting in an enhanced antigen cross-presentation of tumour antigens and subsequent antitumoural immune response.[15] Intratumourally injected tilsotolimod in combination with systemic pembrolizumab or the CTLA-4 inhibitor ipilimumab was investigated in the ILLUMINATE-204 trial for melanoma patients who did not respond to prior PD-(L)1 inhibitor therapy (NCT02644967). The ORR in 49 patients was 22.4% with two CR.[16] In another phase Ib trial, the combination of the TLR9 agonist CMP-001 and pembrolizumab demonstrated an ORR of 23.5% in the dose-finding part I and 17.5% for CMP-001 monotherapy in part II (NCT02680184).[17] In an ongoing phase Ib/II trial with the intratumourally applicated TLR9 agonist cavrotolomid, an ORR of 21% could be determined for patients with advanced solid tumours treated with additional systemic pembrolizumab. In phase II of the trial, patients with advanced cSCC refractory to PD-1 inhibitor are treated with intratumoural cavrotolomid and intravenous cemiplimab (NCT03684785).[18] Via TLR 7/8 and the intracellular receptor retinoic acid-inducible gene I (RIG I) the non-coding RNA CV8102 activates the immune system

Table 1 Ongoing or recently finished clinical trials including patients with cutaneous squamous cell carcinoma refractory to PD-1 inhibitor therapy

ID	Start	End	Design	Intervention/application	Primary/Secondary outcomes
EGFR inhibitors					
EudraCT 2018-001708-12 ('AliCe')	Sep 2018	Ongoing	Multicentre, open-label, single-arm, phase II	Cetuximab 500 mg/m^2 i.v. Q2W + Avelumab 10 mg/kg i.v. Q2W	PO: ORR SO: PFS, OS, DoR, QoL
NCT 03524326	May 2018	April 2023	Multicentre, open-label, single-arm, phase I/Ib	Cetuximab (400 mg/m^2 once, 250 mg/m^2 weekly) i.v. + 3 + 3 dose de-escalation design of the tyrosine kinase inhibitor lenvatinib (24 mg/20 mg/14 mg/10 mg/4 mg daily) p.o.	PO: MTD
Toll-like receptor agonists					
NCT 03684785	Dec 2018	June 2023	Multicentre, open-label, two-part, randomized phase I/phase II	Phase I: Cavrotolimod (TLR 9 agonist, dose determination via 3 + 3 dose escalation for 2, 4, 8, 16, and 32 mg) i.t. and adding pembrolizumab 2 mg/kg Q3W at the second cycle Phase II (for cSCC): Cavrotolimod i.t. + cemiplimab 350 mg Q3W i.v. (dose expansion following a modified Simon 2-stage optimal design)	PO: AE SO: RP2D, ORR, biomarkers (lymphocytes, PD-L1 expression, gene expression)
NCT 03291002	Sep 2017	Feb 2023	Multicentre, open-label, non-randomized, phase I/Ib	non-coding RNA CV8102 (TLR 7/8) (dose escalation for dose levels of 25–600 μg) i.t	PO: MTD, AE SO: TR, DS, survival
Interleukins					
NCT 03901573	Dec 2019	May 2024	Multicentre, open-label phase Ib/ Multicentre, open-label two-armed, non-randomized phase II	Treatment: NT-I7 (rhIL-7-hyFc) (IL-7 agonist) (3 + 3 dose escalation (in phase I)/expansion (phase II) (i.m.) + Atezolizumab (dose escalation/expansion) i.v. Two cohorts: 1 PD-1/PD-L1 inhibitor-naïve 2 PD-1/PD-L1 inhibitor- refractory	PO: MTD/DLT, RP2D, AE SO: ORR, DCR, DOR, PFS, OS, immunogenicity
NCT 04234113	June 2019	Mar 2022	Multicentre, open-label, non-randomized phase I/Ib	SO-C101 (IL-15 agonist) +/− pembrolizumab	PO: DLT, AE, LTA, ECOG PSS SO: plasma concentration SO-C101, ORR, BOR, DOR, CBR, PFS, antibodies to SO-C101
Pathway regulators					
NCT 03590054	Aug 2018	Feb 2022	Single enter, open-label phase I	Abexinostat (HDAC inhibitor) (dose escalation: 20 mg/m^2, 30 mg/m^2, 45 mg/m^2) days 1–4 & 8–11 in 21 day cycle p.o. BID + pembrolizumab 200 mg i.v Q3W	PO: MTD, RP2D, ORR SO: ORR, DoR, PFS, AE
EudraCT Number: 2020-000864-42	?	?	Multicentre, open-label phase II	IFX-1 (anti-C5a monoclonal AB) in different dose regimen (400–1600 mg) +/− pembrolizumab 400 mg Q6W	PO: antitumour activity of IFX-1 (+/− pembrolizumab), MTD, SO: efficacy, safety profile, pharmacokinetics, immunogenicity, QoL
Oncolytic viruses					
NCT 03767348 ('IGNYTE')	Sep 2017	Nov 2024	Multicentre, open-label, non-randomized phase I/II	RP1 (oncolytic HSV-1) i.t. +/− nivolumab i.v. (dose escalation and expansion)	PO: RP2D, AE, DLT, ORR, MTD SO: biologic activity, RP1 levels (urine, blood), CR, DOR, PFS, OS

Table 1 *Continued*

ID	Start	End	Design	Intervention/application	Primary/Secondary outcomes
NCT 02978625	Sep 2017	June 2021	Multicentre, open-label, two-part, single-arm phase II	TVEC (oncolytic HSV-1) (i.t.) (+ nivolumab i.v. if no response after 12 weeks on day 1) Cycles repeat every 21 days for cycle 1 then every 14 days	PO: RR, best ORR SO: RR, PFS, OS, AE, contribution to curative surgery
Vaccination					
NCT 03773744 ('Pelican')	Jan 2020	Dec 2021	Multicentre, open-label, two-armed, non-randomized phase Ib	Single application of Ad-MAGE3 i.m. (, single application of the cyclophosphamide 300 mg/m^2 i.v., arm 1), + pembrolizumab 200 mg i.v. and of MG1-MAGE3 i.v. (and i.t.subsequently, arm 2) (dose escalation)	PO: safety, MTD SO: OR, DC, PFS, DOR
NCT 04160065	Mar 2020	Sep 2021	Multicentre, open-label, non-randomized phase I	IFx-Hu2.0 (plasmid DNA) (0.1 mg) i.t. (different frequencies of application)	PO: AE SO: number major protocol deviation, ORR

AE, adverse effects; DLT, dose-limiting toxicities; BID, bis in die/twice daily; CR, complete response; DOR, duration of response; DS, disease status; ECOG PSS, Eastern Cooperative Oncology Group Performance Status Score; i.m., intramuscular; i.t., intratumoural; i.v., intravenous; LTA, laboratory test abnormalities; MTD, Maximum tolerated doses; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; p.o., per os/oral administration; PO, primary outcome; Q2W/Q3W, once every 2/3 weeks; QoL, Quality of Life; RP2D, recommended phase II dose; RR, Response Rate; SO, secondary outcome; TR, tumour response.

after intratumoural injection. Patients with advanced cSCC refractory to anti-PD-1-inhibitor therapy can be included in an ongoing phase I trial in which they receive CV8102 as monotherapy (NCT03291002, results for cSCC pending).

Interleukins

Endogenous interleukins (IL) number among cytokines and physiologically modulate the immune system by stimulating the release of additional cytokines (e.g. interferon-γ), by activating the ontogeny, maturation (e.g. NK- and T cells by IL-15) and proliferation (e.g. NK- and T cells by IL-2) or maintaining survival (e.g. T cells by IL-7) of immune cells.[19] A recently published phase II trial with 22 melanoma patients showed that the repetitive intratumoural application of the plasmid IL 12 (tavokinogene telseplasmid; tavo) restored the responsiveness to pembrolizumab despite previous anticancer treatment failure. Anti-PD-1 antibody experienced and naïve patients showed an ORR of 41% (36% CR).[20] For SCC, the combined use of IL-7 and PD-1 inhibitors reduced immunosuppressive cell function in both murine and ex vivo human cells resulting in synergistic antitumour effects.[21] An ongoing phase Ib/IIa trial includes both patients with advanced cSCC naïve and refractory to PD-1 inhibitor therapy for combined treatment with intramuscular IL-7 [rhIL-7-hyFc (NT-I7)] and atezolizumab (PD-L1 inhibitor; NCT03901573, results pending). A recently initiated phase I trial includes patients with advanced cSCC refractory to PD-1 inhibitors who receive the IL-15 agonist SO-C101 as monotherapy or in combination with pembrolizumab (NCT04234113, results pending).

Pathway regulators

Histone deacetylases (HDAC) regulate the expression levels of genes by controlling histone acetylation. In tumours, elevated activity of HDAC may misregulate the expression of tumour suppressor genes and/or proto-oncogenes favouring tumour growth. The inhibition of HDAC may influence tumour immunogenicity and 're-sensitize' tumour cells to PD-1 inhibitor therapy.[22] For Merkel cell carcinoma (MCC), the ongoing phase II trial MERKLIN 2 includes patients refractory to PD-(L) 1 inhibitor therapy. Patients receive avelumab in combination with domatinostat (HDAC inhibitor; NCT04393753). Similarly, melanoma patients primary refractory to PD-1 inhibitors receive combined treatment with pembrolizumab and domatinostat in the phase Ib/II trial SENSITIZE (NCT03278665). Patients with advanced cSCC (of the head/neck) refractory to PD-(L)1 inhibitor therapy can be included in an ongoing phase I trial for treatment with pembrolizumab i.v. and different dose scheme of the HDAC inhibitor abexinostat p.o. (NCT03590054, results pending).

An impaired pathway of the tumour suppressor p 53 is a major contributor to the development of cSCC. Murine double minute chromosome 2 (MDM2) is activated in several tumour types and inhibits the function of p53. As antitumour drug, KRT-232 binds to MDM2 and inhibits the MDM2/p53 interaction. Both *in vitro* and *in vivo*, KRT-232 has been shown to inhibit the growth of tumour cells.[23] First results of the clinical use of KRT-232 could be generated in a phase II trial with 11 patients suffering from MCC refractory to PD-L1 inhibitor therapy (NCT 03787602). In interim analysis, ORR was 33%.[24]

The inflammation mediator C5a is part of the complement system. C5a and its receptor C5aR1 contribute to the regulation of squamous carcinogenesis by promoting cancer-associated inflammation. Elevated expression of C5aR1 was determined in SCCs of patients with impaired survival.[25] In mice, inhibition of C5a promoted antitumour efficacy of PD-(L)1 blockade.[26] In the IFX-1-P2.8 trial, the anti-C5a monoclonal antibody IFX-1 will be given in different dose regimens as monotherapy or together with pembrolizumab. IFX-1-P2.8 will include patients with advanced cSCC who have progressed on PD-1 inhibitor therapy.

Oncolytic viruses

Oncolytic viruses are genetically modified viruses that preferentially replicate in tumours and promote immunogenic cell death. The subsequent release of tumour antigens is thought to trigger a generalized host immune effect inducing a systemic antitumour immune response. In 2015, the oncolytic virus talimogene laherparepvec (TVEC), a genetically modified herpes simplex virus type 1 (HSV-1), was approved for the treatment of advanced melanoma. In combination with PD-1 inhibitors, the application of oncolytic viruses induced enhanced T-cell levels and PD-L1 expression both in the injected tumour and in non-injected tumours.[27] In two different ongoing trials (NCT02978625 and NCT03767348) patients with advanced cSCC refractory to prior anticancer therapy receive one of the genetically modified HSV-1 TVEC or RP1 as monotherapy or in combination with PD-1 inhibitors, respectively (results for cSCCs refractory to PD-1 inhibitors pending). In an interim analysis, three of four melanoma patients refractory to PD-1 inhibitors showed immune activation in tumour biopsies, including recruitment of $CD8^+$ T cells and increased PD-L1 expression after exposition to RP1 and nivolumab.[28]

Vaccination

Based on the principles of vaccination, injection of tumour antigens is expected to induce an immune system response. The phase I trial Pelican includes patients with advanced cSCC who have failed standard of care treatment. Patients are treated with different dose scheme of (cyclophosphamide, arm 1) Ad-MAGE-A3, pembrolizumab and MG1-MAGEA3 (NCT03773744). Melanoma-associated antigen 3 (MAGEA3) is one of several cancer-testis antigens that are found on different cancer types and is considered a possible stimulator of the immune system. Ad-MAGE3 is an adenovirus vaccine and MG1-MAGEA3 is an MG1 Maraba oncolytic virus considered to restore the sensitivity to ICI.[29] In another trial patients refractory to standard therapy receive the plasmid DNA IFx-Hu2.0 encoding the streptococcal membrane protein Emm55 (NCT04160065). Preliminary correlative laboratory data of advanced melanoma patients showed an immune response after intralesional injection.[30]

Conclusion

Despite the recent advances in immunomodulatory antitumour therapy, there are currently no approved systemic treatment alternatives for patients with advanced cSCC who have shown partial response or lack of response to PD-1 inhibitor therapy. Ongoing trials on toll-like receptors, ILs, pathway regulators, oncolytic viruses and vaccination constitute complementary approaches to multidimensionally stimulate the immune system in patients with advanced cSCC refractory to PD-1 inhibitors and potentially enhance responsiveness to anticancer therapy.

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CASE REPORT

Development of thoracic sarcoid reactions associated with complete response to anti-PD-1 therapy in a patient with advanced cutaneous squamous cell carcinoma

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Abstract In patients with advanced cutaneous squamous cell carcinoma (cSCC), positive efficacy data were reported for anti-PD-1 antibodies. However, anti-PD-1 treatment is associated with a wide range of immune-related adverse events (irAEs). Here, we report on a 78-year-old woman with a huge cSCC on the right cheek spanning from the temporal to the cervical region with evidence for infiltration of the parotid gland, right masseter muscle and right auditory canal. Ultrasound revealed cervical, submandibular and supraclavicular lymph node metastases on patient's right side. On the basis of a medical hardship application, treatment with pembrolizumab was initiated. After two applications, a dramatic regression of the tumour was observed. At this point, the patient was switched to cemiplimab, which, in the meantime, had become available in Germany. After 3 months on cemiplimab, the tumour-related ulcer on the right cheek showed almost complete regression and all previously affected lymph nodes displayed no evidence for malignancy. Thoracic computed tomography (CT) scans revealed enlarged mediastinal and bilateral hilar lymph nodes assessed as primarily reactive. Three months later, however, mediastinal and bilateral hilar lymph nodes further increased in size, accompanied by radiological alterations of the lung parenchyma. Lymph node biopsies revealed sarcoid reactions (SRs) including fibrotic non-caseating epitheloid cell granulomas surrounded by lymphocytes. Since the patient did not display any clinical symptoms, cemiplimab treatment was continued following a 4-week break. Three months later, CT showed significant regression of the described enlarged lymph nodes and parenchymal lung changes. Twenty months after anti-PD-1 treatment, the patient was still in complete remission. In conclusion, we describe, for the first time, the case of a patient with advanced cSCC who developed disseminated thoracic SRs which were associated with dramatic regression of tumour masses. Thus, as with other irAEs, development of SRs might be indicative of an anti-tumour response to anti-PD-1 therapy.
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Conflict of interest

T.G. has received speakers and/or advisory board honoraria from BMS, Sanofi-Genzyme, MSD, Novartis Pharma, Roche, Abbvie, Almirall, Janssen, Lilly, Pfizer, Pierre Fabre and Merck-Serono, outside the submitted work. L.S. has received speakers and/or advisory board honoraria from BMS, Sun-Pharma, MSD and Novartis. S.P. and C.H.S. have no conflict of interest to declare.

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None.

What does this study add?
Sarcoid reactions may occur during anti-PD-1 therapy and might be indicative of an anti-tumour response in patients with advanced cutaneous squamous cell carcinoma as well.

Introduction

Advanced cutaneous squamous cell carcinoma (cSCC) is a life-threatening malignancy, in particular for patients not eligible for curative surgery or radiation. A relatively novel treatment approach with the immune checkpoint inhibitor (ICI) cemiplimab, a potent monoclonal antibody directed against programmed death 1 protein (PD-1) receptor, has recently been approved as single agent for the treatment of adult patients with metastatic or locally advanced cSCC who are not candidates for curative surgery or radiotherapy.[1] Migden *et al.*[2] reported consistent response rates in phase I and II studies of patients with advanced cSCC managed with cemiplimab. In patients with advanced cSCC, positive efficacy and safety data were also

reported for other PD-1 blockers such as pembrolizumab and nivolumab.[1] The use of ICIs, such as anti-PD-1 blockers, is associated with a wide range of immune-related adverse events (irAEs), frequently including skin toxicities, thyroiditis and pneumonitis.[3] However, sarcoid reactions (SRs) have rarely been reported.[4–8] SRs are similar to sarcoidosis in terms of histology, clinical and radiological findings. The most commonly affected organs are hilar and mediastinal lymph nodes, lung parenchyma and the skin.[4–8] Here, we report the first case of thoracic SRs in a patient with metastatic cSCC successfully treated with anti-PD-1 agents.

Case report

A 78-year-old woman presented with a huge, exophytic and ulcerated tumour on the right cheek and a medical history of hypertensive heart disease. Histopathology revealed a highly differentiated cSCC without perineural invasion. Computed tomography (CT, Fig. 1) scans of the skull and neck showed an expansive, centrally necrotic tumour on the right cheek reaching from the temporal to the cervical region with evidence for infiltration of the parotid gland, right masseter muscle and right auditory canal. Ultrasound revealed cervical, submandibular and supraclavicular lymph nodes suspicious for metastases on the right side. Further staging did not provide evidence for distant metastatic disease. Since the patient refused any surgical approaches, radiotherapy and systemic treatment with an anti-PD-1 antibody were scheduled. Even though cemiplimab had just been approved for the management of cSCC, it was not yet available in Germany. Hence, based on a medical hardship application, treatment with pembrolizumab (2 mg/kg body weight) was initiated. Following two infusions of pemprolizumab, a dramatic regression of the tumour was observed (Fig. 2a,b). Therefore, the plan to additionally apply radiotherapy was abandoned. After the second cycle of pembrolizumab, the patient was switched to intravenous cemiplimab (350 mg) which had become available in Germany in the meantime. After 3 months of therapy with cemiplimab, ultrasound of cervical, submandibular and supraclavicular lymph nodes revealed no evidence for malignancy. Moreover, the prominent tumour-related ulcer on the right cheek (Fig. 2b) showed almost complete regression (Fig. 2c). Thoracic computed tomography (CT) scans showed enlarged mediastinal and bilateral hilar lymph nodes which were assessed as primarily reactive, rather than suspicious for metastatic disease. Further imaging in the context of staging did not show evidence for tumour relapse. Hence, cemiplimab treatment was continued. Three months later, thoracic CT scans revealed progression of mediastinal and bilateral hilar lymph node enlargements, and, in addition, parenchymal lung changes including ground glass opacities and subpleural reticulation (Fig. 3a). Clinical examination and laboratory analyses did not show evidence for infection. In order to exclude any malignant origin of the thoracic lesions, fine needle biopsies were taken. Histology revealed fibrotic non-caseating epitheloid cell granulomas with lymphocytes and multinucleate giant cells (Fig. 4). Serological analyses showed decreased levels of angiotensin converting enzyme (11 U/L, normal range 20–70), increased levels of interleukin 2 receptor (1619 U/L, normal <710), and the ratio of $CD4^+/CD8^+$ cells in the peripheral blood was increased (9.2, normal 0.8–2). Based on imaging and laboratory analyses, a diagnosis of disseminated thoracic SRs was made. Since the patient showed an excellent performance status and no clinical symptoms, cemiplimab treatment was continued following a 4-week break. Systemic therapy with corticosteroids was not conducted. Three months later, thoracic CT revealed significant regression of mediastinal and bilateral hilar lymph node enlargement as well as a decrease in the ground glass opacities with residual evidence for SRs including fibrotic changes (Fig. 3b). Twenty months after completion of 24 cycles of anti-PD-1 treatment, the patient remained in complete remission (Fig. 2d). Hence, a discontinuation of ICI is currently considered and discussed with the patient.

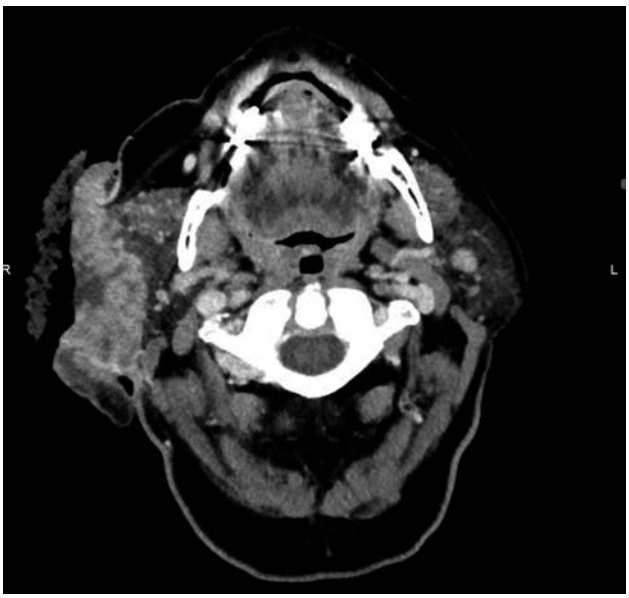

Figure 1 Computed tomography scan of the skull showing an expansive, centrally necrotic tumour on the right cheek reaching from the temporal to the cervical region with evidence for infiltration of the parotid gland, right masseter muscle and right auditory canal.

Discussion

This report highlights that anti-PD-1 agents can achieve impressive early anti-tumour responses in patients with advanced cSCC. However, the very early and prompt tumour regression as well as the long relapse-free survival time described in this case report may be considered unusual. Another peculiar finding

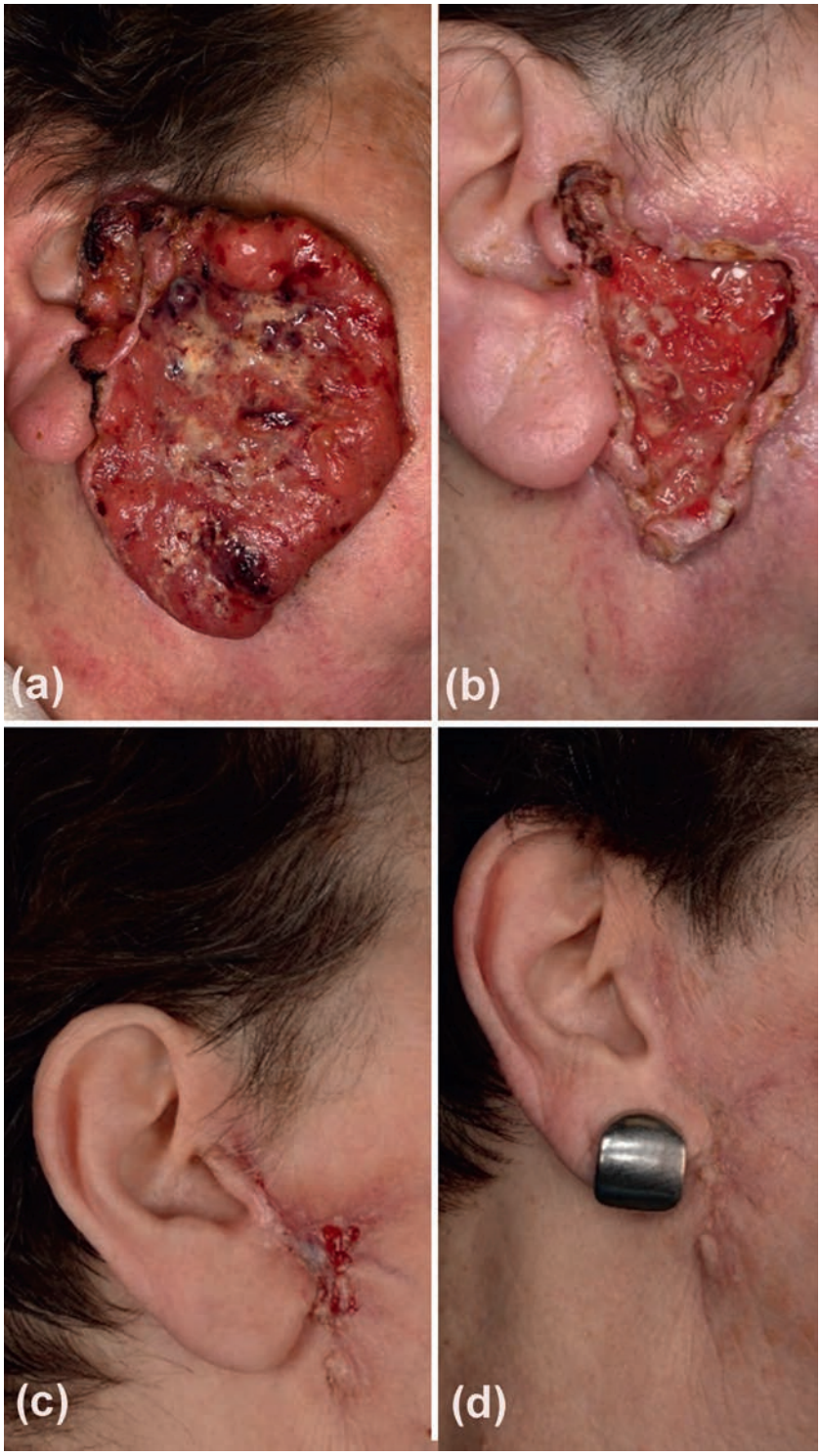

Figure 2 A female patient with a huge ulcerated cutaneous squamous cell carcinoma on the preauricular right cheek (a). After two cycles of pembrolizumab complete regression of the tumour leaving a residual ulcer (b). Three months later, almost complete closure of the ulcer under cemiplimab treatment (c). Complete clearance of the tumour with residual mild pre- and infra-auricular scarring (d).

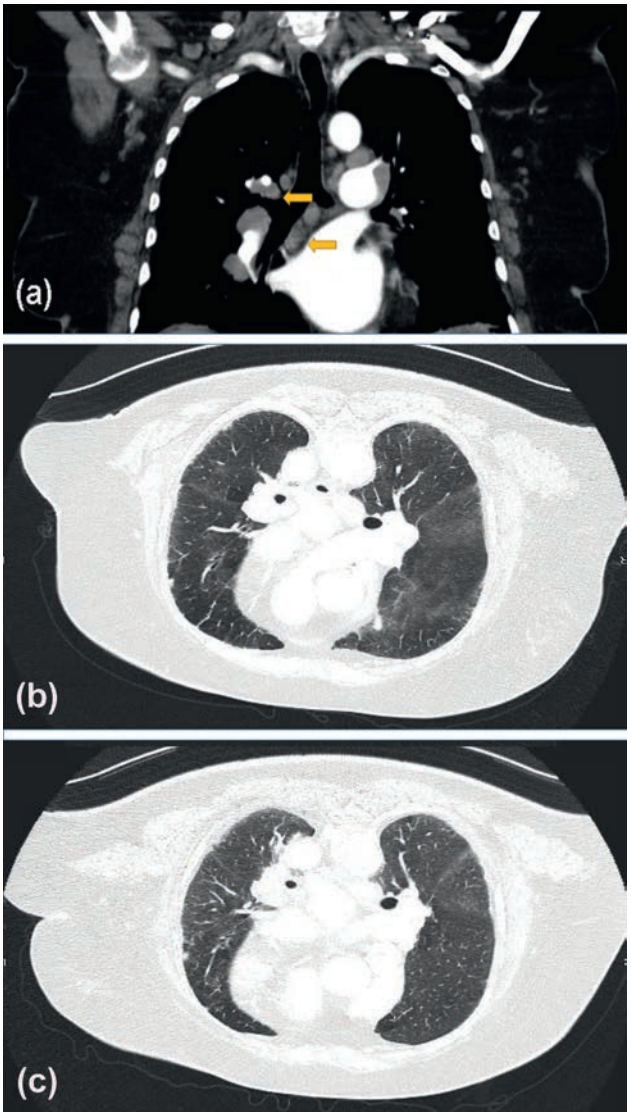

Figure 3 Chest computed tomography showing mediastinal and bihilar lymphadenopathy (a) as well as ground glass opacities and subpleural reticulation in the lungs (b) of a patient with advanced cutaneous squamous cell carcinoma treated with anti-PD-1 agents. Three months later, almost complete resolution of the ground glass opacities (c).

presented here concerns the observed association of anti-PD-1 therapy with the development of disseminated thoracic SRs. Indeed, only anecdotal observations of cSCC associated with granulomatous reactions have been made, and those developed independently of any treatment.[9,10] At the same time, the fact that SRs have been described as possible irAEs of ICI for other entitites together with the close correlation between the start of ICI treatment and the detection of SRs in the present case renders immunotherapy the most likely cause of the granulomatous reactions observed here.[4–8] SRs represent an atypical response pattern characterized by infiltration of lymphocytes and formation of granulomas, mainly in mediastinal and/or bilateral hilar lymph nodes and the lung parenchyma. However, SRs have also been described in other tissues, such as the skin or bone marrow.[4–8] Murthi *et al*.[7] recently reported a wide spectrum of thoracic SLRs, including possible sarcoid-like granulomas in mediastinal and bilateral hilar lymph nodes and in lung tissue, whereas parenchymal reticular opacities and lung fibrosis was also observed in some cases. Their observations indicate that thoracic SRs not only mimic tumour progression but can also be mistaken for pneumonitis, a relatively common irAE of anti-PD-1 agents. Clinically, thoracic SRs that present with symptoms such as coughing and fatigue cannot be discriminated from pneumonitis. As shown above, radiological features of SRs (e.g. ground glass opacities) can also overlap with radiological findings frequently seen in ICI-induced pneumonitis which is defined as the occurrence of respiratory symptoms (cough, dyspnoea etc.) together with newly developed inflammatory thoracic lesions revealed by CT scans during immunotherapy, after the exclusion of infections, tumour progress or other reasons.[5,6,8,10] Indeed, the correct classification of SRs can also be challenging, since they may mimic disease progression. Together, complete and precise clinical and radiological assessment is required for decision-making on treatment and in order to prevent unnecessary discontinuation of potentially beneficial immunotherapy.[11–13]

In the current literature, ICI-induced SRs are increasingly reported in various other cancer entities, in particular in malignant melanoma.[4–8,11–13] Notably, SRs have also been observed in patients treated with BRAF and/or MEK inhibitors.[7] The pathogenesis of ICI-induced SRs is unclear. However, an increase of the PD-1 ligand may lead to unlocking of cytokine production by activated T lymphocytes present in sarcoid-like lesions as well as in the peripheral blood. In fact, removing the brakes on overactivated T cell receptors through inhibition of PD-1 together with stimulation of interferon-γ secretion could directly cause SRs.[5,6] Even though anti-PD-1 agents have been used for the treatment of cSCC for several years, ICI-induced SRs have been reported only once in a patient who developed disseminated cutaneous granulomatous tissue reactions after cSCC nodules on the left lower leg had completely regressed following four cylces of pembrolizumab.[4] Notably, many cases including the on presented here suggest that the occurrence of SRs may be associated with an anti-tumour response.[11–15] In a retrospective investigation of 119 patients who received ipilimumab, the 20 patients showing evidence for irAEs on CT scans, including SRs, had a significantly better response compared to the 99 patients without irAEs.[13] Moreover, in a multivariate analysis, Murthi *et al*.[7] showed that the frequency of metastatic progression was significantly lower in patients with SRs than in those without. Consequently, a significant survival advantage was observed in patients

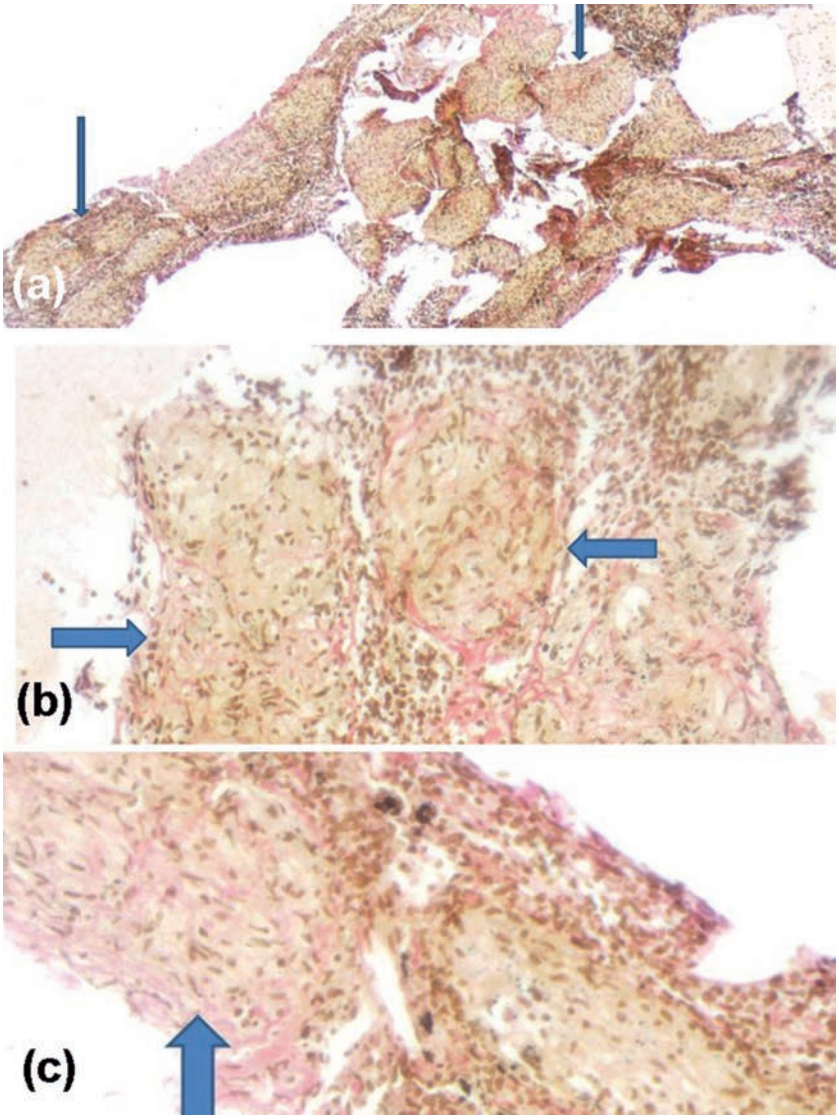

Figure 4 Mediastinal lymph node tissue obtained by fine needle puncture. Elastica-van-Gieson (EvG) stain shows loss of normal lymph node architecture and nodular alteration with partly confluent epitheloid cell granulomas (arrows; magnification: ×40; a). On higher magnification (×100, EvG), there were fibrotic (arrow) non-caseating epitheloid cell granulomas with abundance of lymphocytes at the borders (b). Confluent epitheloid cell granulomas, marginal lymphocytes and formation of collagen fibres in the periphery (magnification: ×200; c).

with SRs compared to those without.[7] Thus, when treatment with ICI induces SRs together with significant anti-tumour efficacy, it may be prudent to continue immunotherapy and therapeutically target SRs only in severe symptomatic cases.

Taken together, for the first time, we report on a patient with advanced cSCC who developed disseminated thoracic SRs associated with dramatic regression of both primary tumour masses as well as lymph node metastases. As with other irAEs such as vitiligo in melanoma patients, the development of SRs might actually indicate anti-tumour response.

Acknowledgement

The patient in this manuscript has given written informed consent to the publication of their case details.

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CASE REPORT

Checkpoint immunotherapy of cutaneous squamous cell carcinoma in patients suffering from chronic lymphocytic leukaemia: divergent outcomes in two men treated with PD-1 inhibitors

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Abstract Cutaneous squamous cell carcinoma (cSCC) numbers among the most common types of skin cancer and is known as one of the cancer entities with the highest mutational burden among all solid tumours. Due to the positive correlation between mutational burden and response rate to inhibitors of the programmed cell death 1 (PD-1), those inhibitors are considered promising candidates for the systemic therapy of cSCC. Recently, the PD-1 inhibitors pembrolizumab, nivolumab and cemiplimab demonstrated efficacy in the systemic treatment of locally advanced or metastatic cSCC leading to the approval of cemiplimab by the FDA (U.S. Food and Drug Administration) in 2018 and the EMA (European Medicines Agency) in 2019. Patients with haematological malignancies tend to develop skin cancers of high aggressiveness, enhanced cumulative recurrence rate and higher rates of metastases with subsequent death. Chronic lymphocytic leukaemia (CLL) is the most frequent type of leukaemia in the United States and Europe with the majority of patients older than 50 years of age. This neoplasm predominantly originates from B -cells leading to an impaired immune system of the patient. Although CLL is a B-cell malignancy, studies have also described the involvement of T cells in the pathogenesis and progression of the disease with contradictory findings on the effects of PD-1 inhibitors in CLL. Due to their underlying hematologic malignancy, these patients have commonly no access to PD-1 inhibitor trials for treatment of advanced cSCC. We report on two patients with locally advanced or metastatic cSCC. Both patients had been suffering from a CLL for many years without indication for treatment. Despite a potential immunosuppressive state of the patients due to their CLL, both were treated with the PD-1 inhibitor pembrolizumab resulting in different therapy outcomes.
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Conflict of interest

E. Livingstone served as consultant and/or has received honoraria from Amgen, Actelion, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Janssen, Medac, Sanofi, Sunpharma and travel support from Amgen, Merck Sharp & Dohme, Bristol-Myers Squibb, Amgen, Pierre Fabre, Sunpharma and Novartis, outside the submitted work. L. Zimmer served as consultant and/or has received honoraria from Roche, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Novartis, Pierre Fabre, Sanofi, and Sunpharma and travel support from MSD, BMS, Amgen, Pierre Fabre, Sunpharma, Sanofi and Novartis, outside the submitted work. G. C. Lodde has received travel support from Sun Pharma, outside the submitted work. A. Roesch declares research support from Novartis, BMS and Adtec, non-financial support from Amgen, Roche, Merck/MSD, Novartis, BMS, TEVA, Adtec, and personal fees from Merck /MSD. D. Schadendorf reports personal fees and non-financial support from Sanofi, during the conduct of the study; personal fees and non-financial support from Roche/Genentech, grants, personal fees, non-financial support and other from BMS, personal fees and non-financial support from Merck Sharp & Dohme, personal fees and non-financial support from Merck Serono, grants,

personal fees and non-financial support from Amgen, personal fees from Immunocore, personal fees from Incyte, personal fees from 4SC, personal fees from Pierre Fabre, personal fees from Array BioPharma, personal fees from Pfizer, personal fees from Philogen, personal fees from Regeneron, personal fees from Nektar, personal fees from Sandoz, grants, personal fees, non-financial support and other from Novartis, outside the submitted work. S. Ugurel declares research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, Novartis and Roche, and travel support from Bristol Myers Squibb, and Merck Sharp & Dohme. The other authors declare no conflict of interests.

Funding source

None.

What does this study add?

- Patients suffering from haematologic malignancies tend to develop skin cancers of high aggressiveness but are commonly excluded from programmed cell death ligand 1 (PD-1) inhibitor trials.
- Both patients presented in this report suffered from cutaneous squamous cell carcinoma and chronic lymphocytic leukaemia but showed different clinical courses of diseases under systemic treatment with PD-1 inhibitors

Case reports

Case 1

A 76-year-old man was first diagnosed with a cutaneous squamous cell carcinoma (cSCC) of the head in November 2016. Prior to this diagnosis, the patient had been treated with photodynamic therapy in 2015 due to extensive actinic keratosis on the head. The primary cSCC had been completely excised elsewhere and wound defect closure had been performed by a rotation flap. The patient gradually developed sharply delineated, extensive, moist erosions with singular crusts and ulcerations nearly covering the whole capillitium with predominance of the left side. After histological confirmation of cSCC, a positron emission tomography/computed tomography in April 2017 revealed no further sites of metastases. The patient received local radiotherapy of the capillitium and regional lymph nodes with 5 × 2 Gy (cumulative dose 60 Gy) from April to June 2017. While receiving this radiotherapy, two nodules appeared on the left medial eyelid and on the right cheek both suspicious of tumour metastases. After biopsy and histopathology, both nodules could be diagnosed as metastases of the cSCC in June 2017. Those nodules lacked expression of programmed cell death ligand 1 (PD-L1) with viable tumour cells stained positive in <1%.

The patient was additionally suffering from a chronic lymphocytic leukaemia (CLL), type B-cell-lymphoma Binet A, chromosomal alteration 14q, first diagnosed in March 2010. According to regular consultations in an external department of haematology, there was no indication for systemic treatment. Due to the underlying CLL disease, the patient could not be enrolled into any therapy trial for his advanced cSCC. Based on the recommendation of our interdisciplinary tumour board, a PD-1 inhibitor therapy with pembrolizumab 2 mg/kg Q3W (≙130 mg) was initiated in July 2017. Prior to treatment initiation, the total number of leukocytes was 5.75/nL. Despite a clinically visible reduction of cutaneous metastases in the face, nodules on the occipital capillitium appeared that were histologically confirmed as metastases in October 2017. Additionally, an enlargement of cervical lymph nodes was determined in October 2017. According to our interdisciplinary tumour board and the consultation of the attending department of haematology, the treatment with pembrolizumab was continued until November 2017. Additionally, local radiotherapy of the head was performed in December 2017. After a cumulative radiation dose of 16 Gy, the patient declined further radiotherapy due to painful sensitivity disorders. In January 2018, the cutaneous tumour lesions as well as the cervical and mediastinal lymph nodes further progressed. At the same time, the patient developed increased leukocyte counts of 30.82/nL, paralleled by a decrease of haemoglobin of 6.5 g/dL. The patient refused further treatment and subsequently died at home in January 2018 (Fig. 1).

Case 2

A 77-year-old man had been suffering from multiple progressively growing cSCC with tumour depths ranging from 1.5 to 9.0 mm since first diagnosis in September 2016. In total, ten cSCCs could be recapitulated, eight on the head and two on the arms or legs. After various surgical and topical treatments, the patient was referred to our Skin Cancer Unit in June 2018 for re-evaluation of systemic therapy.

The patient additionally had a history of multiple cancer diagnoses including CLL (type B-cell-lymphoma Binet A, first

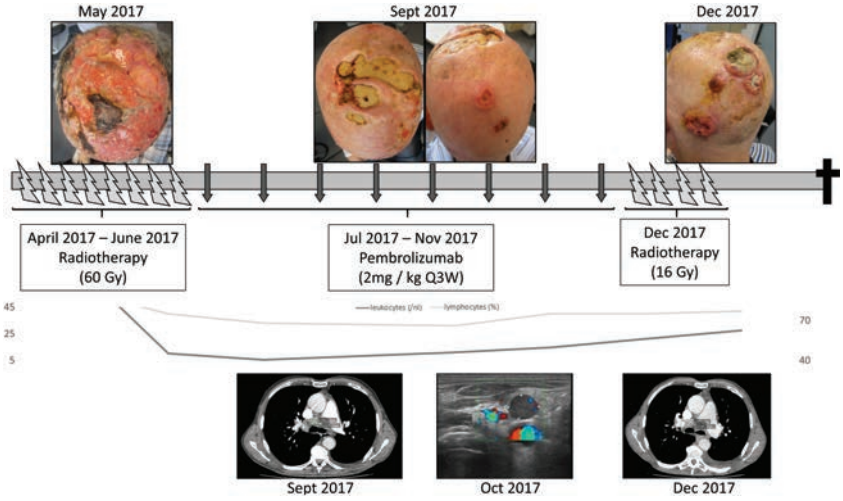

Figure 1 Time course of patient 1. Upper part of the figure: Representative pictures depicting regression and progression of histologically confirmed cutaneous squamous cell carcinoma (cSCC) on the central and dorsal capillitium before, during and after PD-1 inhibitor therapy and radiotherapy, respectively [bright grey arrows: radiotherapy with 30 gray (Gy), and 16 gray (Gy), respectively, dark grey arrows: eight applications of the PD-1 inhibitor Pembrolizumab with 2 mg/kg bodyweight (≙ 130 mg) every third week (Q3W)]. Middle part of the figure: time course of leukocyte levels (in number per nl, dark grey, left *y*-axis) and lymphocytes (in % of leukocytes, bright grey, right *y*-axis). Lower part of the figure: two CT pictures of the thorax with progressively growing mediastinal lymph nodes (left picture: representative lymph node 21.6 mm × 29.3 mm in September 2017, right picture: representative lymph node 27.2 mm × 40.5 mm in December 2017). Central picture: Ultrasound showing hyperechoic and hypovascular representative cervical lymphnodes suspicious of malignant infiltration (Neither the cervical nor the mediastinal lymph nodes were histologically confirmed due to reduced condition of the patient).

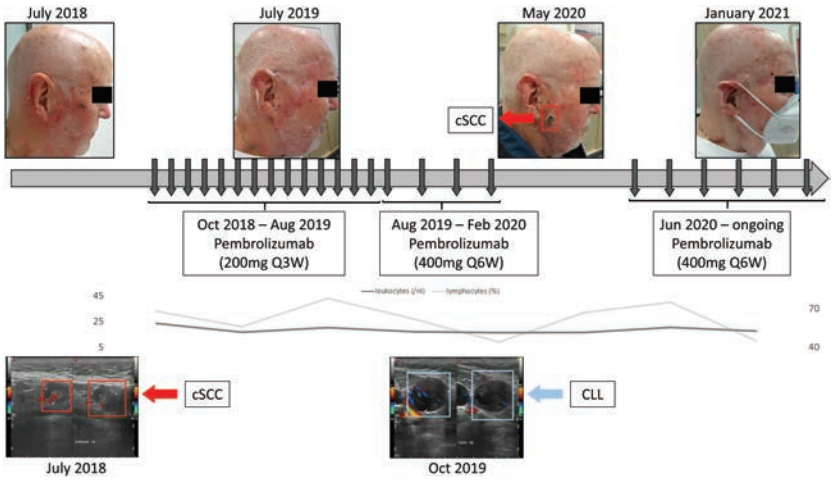

Figure 2 Time course of patient 2. Upper part of the figure: Representative pictures depicting regression and progression of histologically confirmed cutaneous squamous cell carcinoma (cSCC, red rectangle depicting representative cSCC responding to therapy) before, during and after PD-1 inhibitor therapy [grey arrows: 24 applications of the PD-1 inhibitor pembrolizumab every third week (Q3W) and every sixth week (Q6W), respectively]. Middle part of the figure: time course of leukocyte levels (in number per nl, dark grey, scale on the left *y*-axis) and lymphocytes (in % of leukocytes, bright grey, scale on the right *y*-axis). Lower part of the figure: Ultrasound showing hyperechoic and hypovascular submandibular/cervical lymphnode metastases of cSCC (red rectangle, histologically confirmed) and chronic lymphocytic leukaemia (CLL, blue rectangle, histologically confirmed).

diagnosed in 09/2004), ductal breast cancer [pT1c N1 (3/19), first diagnosed 09/2009, treated with radiochemotherapy and tamoxifen], and prostate adenocarcinoma (T1c, Gleason score 3 + 4 = 7a, first diagnosed 07/2007, treated with brachytherapy). Under regular clinical and laboratory follow-up control, there had been no indication for systemic treatment of the CLL; all other cancers remained disease-free with no systemic treatment indication after the initial therapy.

When first presenting at our Department in July 2018, the patient showed multiple tumour nodes with strong squamation and crusts predominantly disseminated on the capillitium, the temporal region, the forearms and upper legs. Additionally, multiple enlarged lymph nodes imposed in the right cervical, abdominal and mediastinal regions diagnosed sonographically and in CT scans. One of the suspicious cervical lymph nodes could be surgically excised. A metastasis of the cSCC could be confirmed histologically that strongly expressed PD-L1 (viable tumour cells stained positive in >20%). Due to the underlying CLL, the patient could not be enrolled into any therapy trial. Our interdisciplinary tumour board recommended systemic treatment with the PD-1 inhibitor pembrolizumab, which was subsequently initiated in October 2018 with a fixed dose of 200 mg Q3W. After initial stable disease, a partial response of the multiple lesions on the capillitium was first documented in July 2019. In August 2019, the pembrolizumab dosing was modified to 400 mg Q6W.

After a long-term stabilization in size of the enlarged cervical, abdominal and thoracic lymph nodes confirmed in repetitive CT scans, growth progression of a cervical lymph node was sonographically determined in October 2019. A clear infiltration of CLL cells was confirmed histolopathologically confirming progression of the CLL. There were no indications for progression of the other malignancies. According to the attending department for haematology, there was still no need for systemic treatment of the CLL. By request of the patient, the pembrolizumab therapy was suspended from March 2020 to June 2020 after 14 applications of pembrolizumab 200 mg Q3W and four applications of pembrolizumab 400 mg Q6W due to the COVID-19 pandemic. In May 2020, he developed a rapidly growing nodule on the face that was subsequently excised and histologically confirmed as cSCC. After a reduction in COVID-19 incidence, pembrolizumab therapy at 400 mg Q6W was re-induced in June 2020. Currently, the patient is still on treatment with stable disease of both his active cancers, cSCC and CLL (Fig. 2).

Discussion

While patient 2 had a stable number of leukocytes under therapy with pembrolizumab, patient 1 showed an increase under treatment with pembrolizumab indicating a progression of the CLL. In patient 2, a progression of the CLL could be confirmed histologically under PD-1 inhibitor therapy. Both patients showed (at least temporarily) progression of CLL under PD-1 inhibitor therapy. Therapeutic effect of PD-1 inhibitors for CLL is currently under investigation but single application of PD-1 inhibitor has been suggested possibly insufficient to control CLL.[1,2]

The aggressiveness of skin cancers in patients with concomitant haematological malignancies has been mainly attributed to the impaired function of their immune system[3–5] possibly modulating response rate to PD1-inhibitor therapy as well. A recently published analysis with 84 patients could underline that PD-1 inhibitor therapy in patients with haematological malignancies and advanced cSCC is significantly impaired compared to patients without haematological malignancies. Best objective response was limited to 26.7% (in contrast to 50% in patients without CLL). Additionally, no significant change in the number of leukocytes could be determined during PD-1 inhibitor therapy.[6,7] Both patients reported benefitted from therapeutic response of the cSCC to PD-1 inhibitor therapy. Still, patient 2 showed progression of cSCC after PD-1 inhibitor therapy interruption due to COVID-19 pandemic.

Clinical studies are mandatory to further investigate the therapy outcome of patients with advanced skin cancer and concomitant haematologic disease.

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The patients in this manuscript have given written informed consent to publication of their case details.

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CASE REPORT

Treatment of metastatic cutaneous squamous cell carcinoma in a solid organ transplant recipient with programmed death-1 checkpoint inhibitor therapy

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Abstract Limited data exist on the use of immune checkpoint inhibitors (ICI) for the treatment of metastatic cutaneous squamous cell carcinoma (CSCC) in solid organ transplant recipients (SOTR). We report a case of a SOTR who developed metastatic disease following multiple surgeries, three cycles of adjuvant radiotherapy, and minimization of immunosuppression. He was subsequently treated with pembrolizumab and achieved a complete response. However, the patient developed ICI-induced allograft rejection requiring therapy discontinuation. The allograft was salvaged following IVIg and steroids. The patient developed recurrent disease which failed rechallenge with pembrolizumab but achieved a partial response following cemiplimab administration. This case illustrates the potential to treat metastatic CSCC in a SOTR with anti-programmed death-1 therapy and preserve graft function despite allograft rejection.
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Conflict of interest

KAO has no conflicts of interest to declare. CDS is a steering committee member for Castle Biosciences; a steering committee member and consultant for Regeneron Pharmaceuticals; a consultant for Sanofi; has received research funding from Castle Biosciences, Regeneron Pharmaceuticals, Novartis, Genentech, and Merck, and is a chair for NCCN.

Funding sources

None

What does this study add?

- This case illustrates the slowly progressive nature of a subset of cutaneous squamous cell carcinomas. Our patient experienced six local recurrences over a 10-year period, finally resulting in both in-transit and distant metastasis.
- The case illustrates successful treatment of immune checkpoint inhibitor-induced renal rejection in a transplant recipient with metastatic cutaneous squamous cell carcinoma.
- The case illustrates a response to cemiplimab following failure of rechallenge via a same-class drug (pembrolizumab).

Introduction

Cutaneous squamous cell carcinoma (CSCC) is the most common malignant neoplasm affecting solid organ transplant recipients (SOTR).[1] Long-term immunosuppression affects the microanatomical distribution of intra- and peritumoural immune infiltrates of CSCC,[2] and immunosuppressed patients have an increased risk of metastatic disease.[3] Metastatic CSCC and immunosuppression is associated with a two-fold increased risk of death.[3] While anti-programmed death-1 (PD-1) therapies (including cemiplimab and pembrolizumab approved in the United States, cemiplimab in Europe) are indicated for patients with recurrent and/or metastatic CSCCs that progress despite treatment with surgery and radiation, the efficacy and safety of PD-1 therapy in SOTR is not well-studied. SOTR recipients were excluded from prior clinical trials due to concerns of allograft rejection.[4] A systematic review of 57 cases of SOTRs (32 renal) undergoing immunotherapy reported a rejection risk of 37% which led to death in 14% of patients.[5] Three summary analyses reported similar results.[6–8] A clinical trial is ongoing evaluating renal transplant patients with unresectable/metastatic cancers treated with tacrolimus, nivolumab, and ipilimumab (NCT03816332). Another trial is examining cemiplimab in renal/stem cell transplant patients and includes peri-infusional

IRB Approval Status: None.

prednisone (NCT04339062) in an attempt to minimize the risk of graft rejection. No guidelines or consensus statements exist on the use of PD-1 therapy in SOTR with advanced CSCC.

A 68-year-old Caucasian man with polycystic kidney disease status post living donor renal transplant initially presented at age 56, 7 years post-transplant, with biopsy-proven moderately-differentiated CSCC on the left central cheek. The patient had a history of aggressive CSCC on the scalp requiring radiation. The cheek CSCC was considered a new primary. Immunosuppression included sirolimus and mycophenolate mofetil. He had switched from tacrolimus to sirolimus and been weaned from prednisone following his scalp CSCC. The cheek tumour was excised with clear margins [vertical sections (VS)]. Fourteen months later, a local recurrence (LR) required two excisions to achieve clear margins (VS). Three months later, the patient developed a second LR excised with a 0.5-cm clinical margin. Pathology revealed a positive margin with perineural invasion (VS). It was re-excised, showing poorly differentiated CSCC at one margin (VS) and multifocality of tumour growth with skip areas between foci. VS showed a positive deep margin on the third attempt to excise (0.6 cm clinical margin) this second LR. A 6 × 5 cm skin graft was placed and the patient received salvage radiotherapy (Fig. 1).

He was disease-free for 3 years until a recurrence of poorly differentiated CSCC developed within the graft. This third LR was cleared with four stages of Mohs micrographic surgery (MMS; Fig. 2). Multiple foci of perineural invasion were noted.

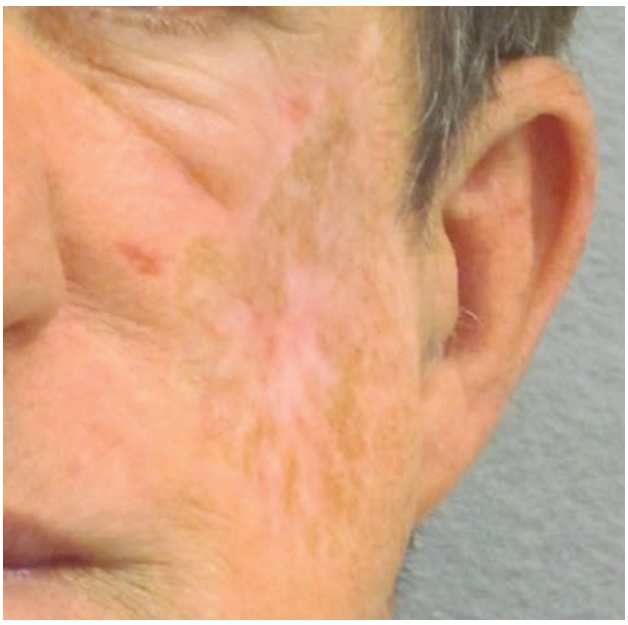

Figure 1 Clinical appearance following excision and radiotherapy for second local recurrence.

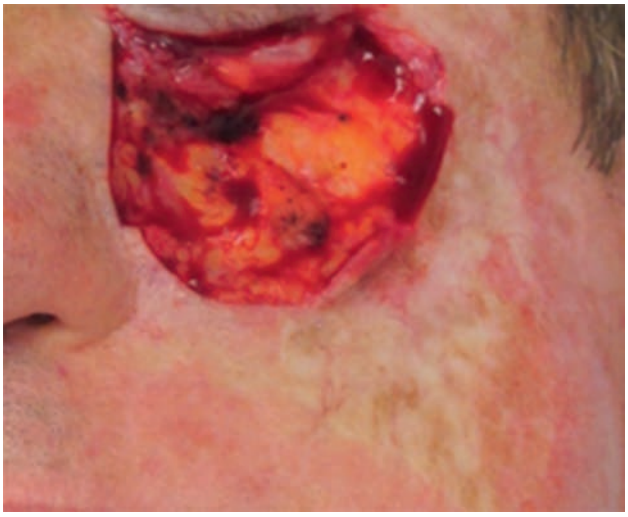

Figure 2 Defect following Mohs micrographic surgery for third local recurrence.

A graft was placed. Since much of the previously radiated zone was re-excised during MMS, he was able to receive a second full course of adjuvant radiation. The MMS margin was narrowest at the lower eyelid margin; this region also received relatively less radiation. The patient noted retraction and swelling of the area. Though biopsied and benign, it required three surgeries over 2 years to be corrected. During the third surgery, tissue revealed CSCC. MRI identified focal enhancement just lateral to the orbit. Given this fourth LR of histologically aggressive CSCC, a large surgery was undertaken with wide local excision encompassing all previously treated areas, orbital exenteration, partial maxillectomy, superficial parotidectomy, and free-flap reconstruction. Although both maxilla and orbit were negative for tumour, the tumour was present <0.1 cm from the lateral and medial soft tissue margins of the orbit. Thus, a third cycle of radiation was completed.

He remained clear for a year and then developed a fifth LR with two foci adjacent to the flap. The preauricular region had a growth pattern of single-cell spread with nests of 2–10 cells and large-caliber perineural invasion, requiring four MMS stages to clear (Fig. 3). Above the brow was cleared with two MMS stages.

Four months later (8 years postpresentation), he developed a 1 cm in-transit metastasis on the mandibular angle, 3–4 cm from the prior surgical site (poorly differentiated SCC with large-caliber perineural invasion measuring 0.35 mm). Positron Emission Tomography and Computed Tomography (PET-CT) revealed concurrent LR of the primary tumour into the sinuses beneath the flap and potentially distant metastasis to both liver and lungs.

Given extensive disease and multiple failures of surgery + radiation, immunotherapy was recommended (although not yet approved for CSCC and risk of allograft rejection was known).

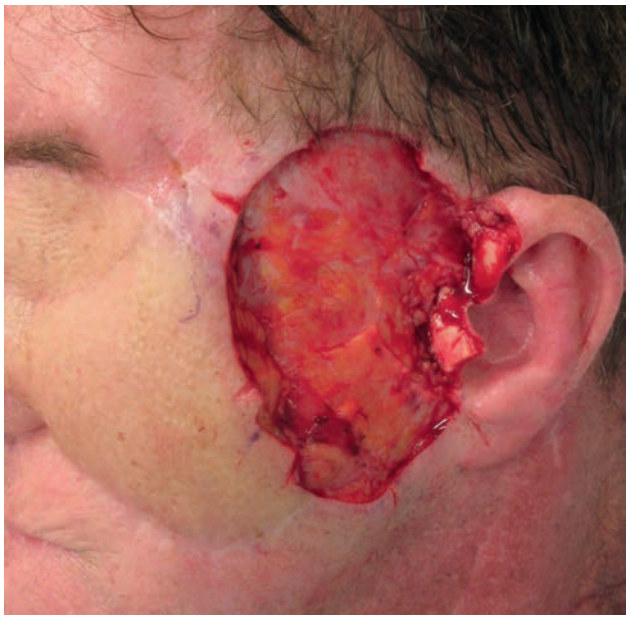

Figure 3 Defect following Mohs micrographic surgery for fifth local recurrence.

He began off-label pembrolizumab as cemiplimab was still in clinical trials. Re-staging after 8 months demonstrated a complete response (CR) by Response Evaluation Criteria in Solid Tumours (RECIST) criteria. However, at the same time, his creatinine increased. Renal biopsy confirmed humoral and T cell-mediated acute rejection, presumably a result of immunotherapy. Pembrolizumab was discontinued and rejection was treated with high-dose steroids + IVIg.

PET 8 months following discontinuation of pembrolizumab showed thickening of the right hemidiaphragm, suspicious for metastasis. Repeat PET after 3 months identified new lung nodules which were biopsy-confirmed metastatic CSCC. Pembrolizumab rechallenge was attempted. A dynamic prednisone dosing schedule (40 mg day prior to infusion, 20 mg daily for 5 days, then 7.5 mg daily) was chosen to mitigate the chance of worsening renal rejection. Staging PET 3 months later identified worsening pulmonary disease and pembrolizumab was discontinued. He was trailed on carboplatin and cetuximab, however, staging PET during therapy noted progression of disease to ribs and chest wall. He developed symptomatic chest wall pain requiring palliative radiation. Cetuximab was discontinued, and he was started on cemiplimab with the same peri-infusional prednisone schedule above. PET staging noted a partial response (PR) by RECIST to cemiplimab. He remains on cemiplimab with stable renal function.

This case illustrates the slowly progressive nature of a subset of CSCC. This patient's CSCC has afflicted him for over 10 years. He experienced six LRs, the last of which was concurrent with in-transit and distant metastasis. Similar to immunocompetent individuals, risk factors for the development of aggressive CSCC in SOTR include perineural invasion and poor differentiation.[9]

The primary tumour and first two recurrences were managed with six surgeries using standard vertical sectioning for margin assessment. Though this was allowable at the time, current NCCN recommendations advise complete circumferential peripheral and deep margin assessment (CCPDMA:MMS or Tubingen technique) to manage large, aggressive CSCCs.[10] MMS + radiation failed at the narrow eyelid margins but otherwise controlled his local disease. The tumour also appeared resistant to radiation with infield recurrences after each of the three courses. Minimization of immunosuppression and switching from a calcineurin inhibitor to a mammalian target of rapamycin inhibitor was done. Although these measures did not prevent the formation of this aggressive CSCC nor its refractory course, they may have slowed progression. Unfortunately, his CR with pembrolizumab could not be maintained since it was accompanied by allograft rejection and drug discontinuation. It is interesting that while rechallenge with pembrolizumab was ineffective, cemiplimab, a same-class PD-1 inhibitor, resulted in response.

The PD-1 axis plays a role in preserving graft tolerance. The T cells produced following administration of PD-1 inhibitors act against both tumour antigens and donor alloantigens.[11] This leaves patients with significant risk for allograft rejection.[11] Four systematic reviews have evaluated immune checkpoint inhibitors (ICI) therapy in SOTR, with allograft rejection ranging from 37% to 41%.[5–8] Median time to rejection was 21 days.[8]

Limited literature exists evaluating cancer outcomes following PD-1 therapy for CSCC in SOTR.[5–8,11–16] A study of seven SOTR with advanced CSCC treated with PD-1 inhibitors reported three patients with PR, one CR, one stable disease, and two deaths following tumour progression.[12] Only one patient demonstrated evidence of allograft rejection following cemiplimab, who had a previous history of rejection. This is in line with a systematic review, noting history of prior allograft rejection to be associated with higher rates of rejection following ICI.[7] Five study patients received tumour sequencing, all demonstrating high tumour mutational burdens (TMB).[12] SOTR often have a higher TMB from chronic immunosuppression,[17] and high TMB predicts improved efficacy following ICI therapy.[18]

The success of ICI is closely connected with mechanisms of immune control at the primary tumour site.[2] Our patient obtained CR with pembrolizumab, however, on rechallenge, he did not respond. Yet, when he was treated with another PD-1 inhibitor, cemiplimab, he achieved PR. A study evaluating the comparative efficacy of cemiplimab versus other systemic treatments for CSCC found cemiplimab to have benefits in overall survival and progression-free survival versus pembrolizumab.[19] Further research must be done to elucidate the complex mechanisms underlying successful treatment using PD-1 inhibitors,

especially in SOTR.[20] Although more data are urgently needed on PD-1 therapy for advanced CSCC in SOTR, we surmise immunotherapy holds promise for a number of patients following failure of surgery and radiation. We suspect that our patient would have succumbed to his disease by now without the use of PD-1 therapy. Optimal treatment regimens will minimize T cell-mediated alloreactivity and maximize the tumour-specific T cell response.[11]

As we anxiously await the results of ongoing trials including whether peri-infusional prednisone is protective, the marked risks of allograft rejection (including a death risk likely exceeding 10%) must be clearly discussed with the patient and clinicians must carefully evaluate each case on an independent basis.

Acknowledgement

The patient in this manuscript has provided written informed consent to the publication of their case details.

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CASE REPORT

Value of cemiplimab in progressive metastatic cutaneous squamous cell carcinoma after kidney transplantation: a case report

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Abstract Cutaneous squamous cell carcinoma (CSCC) is the most frequent post-transplant tumour entity resulting from immunosuppression treatment that is needed to prevent organ rejection. Solid organ transplant (SOT) recipients are at higher risk for CSCC and vulnerable for aggressive disease or a fatal course. Here, we report on a case of post-kidney transplant metastatic CSCC, demonstrating efficacy of cemiplimab in achieving complete remission after previous disease progression under cetuximab treatment. Unfortunately, the patient developed severe pneumonia, which was only later diagnosed as cemiplimab-associated pneumonitis. Due to a rapidly evolving septic condition, intensive care treatment was required and resulted in a fatal outcome. The patient's transplant remained intact, yet first-line treatment of advanced CSCC, such as with cemiplimab, should be weighed critically in SOT recipients, as transplant rejection may occur. However, the present case underlines the feasibility of cemiplimab as a second-line treatment option in this patient collective.

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Conflict of interest

CG is a member of the advisory board of and has received honoraria and travel expenses from Amgen, BioNTech, BMS, GSK, Immunocore, MSD, Novartis, Pierre-Fabre, Roche, Sanofi and Sysmex. CG is the co-founder of Dermagnostix.

Funding source

None reported.

What does this study add?

- Kidney transplant recipients are at high risk for advanced cutaneous squamous cell carcinoma.
- Second-line cemiplimab is a feasible treatment option in selected patients.
- First-line cemiplimab should be critically weighed against risk of transplant rejection.
- Close consultation with a transplant nephrologist and thorough discussion with the patient is indispensable.

Case presentation

A 69-year old woman presented at University Skin Cancer Center Hamburg with two rapidly evolving subcutaneous tumour masses in the left axilla and the dorsal left forearm in April 2019. She had been previously diagnosed with incompletely resected cutaneous squamous cell carcinoma (CSCC) of the left axilla (G2, pT3, R1).

Her medical history was most notable for an allogenic renal transplantation in 2004. She had received immunsuppressive treatment with tacrolimus, mycophenolate mofetil and methylprednisolone for prevention of organ rejection since (Fig. 1). Further dermatological history included multiple CSCC in various locations over the course of several years. Among these, recurrent sternal CSCC (G3, pT3, L0, V1 and Pn1), ulcerated muscle-infiltrating CSCC (G3, pT3, L0, V0 and Pn0) at the upper left back and supraclavicular CSCC (G3, pT3, L0, V0 and Pn0) were remarkable.

Upon presentation to our centre, suspicious pleural foci were detected in computed tomography (CT; Figs 1 and 2). The interdisciplinary dermatological tumour board strongly suspected metastatic disease, possibly originating from multiple previously resected CSCC tumour sites. Surgical exploration and tumour reduction in the left axilla revealed recurrent multifocal subcutaneous CSCC infiltrates, most suitably representing local recurrence at the site of prior tumour resection, and lymph node metastases without capsule-penetrating growth. Due to

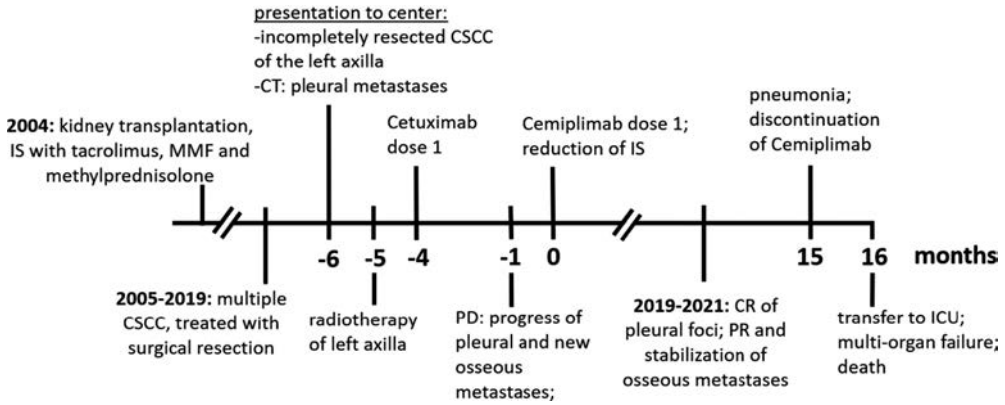

Figure 1 Timeline illustrating the course of a kidney transplant recipient with metastatic CSCC. Periods of years are indicated where applicable. Months from start of cemiplimab treatment are depicted below the timeline. CR, complete remission; CSCC, cutaneous squamous cell carcinoma; CT, computed tomography; ICU, intensive care unit; IS, immunosuppression; MMF, mycophenolate mofetil; PD, progressive disease; PR, partial remission.

infiltration of the left axillary vein and brachial plexus, it was not possible to completely resect the tumour.

Histopathological analysis after exstirpation of the tumour mass at the dorsal left forearm identified SCC without precursor lesions and without connection to the overlying epidermis, most likely representing a metastasis, rather than primary CSCC. CT-guided biopsies of the pleural lesions showed infiltrates of poorly differentiated SCC. TP53 gene sequencing analysis confirmed pleural metastases to exhibit the same point mutation as the axillary CSCC lesion.

Together, the patient was classified stage IVA (pT3 pN3b M1) according to the AJCC 2017 classification system and radiotherapy of the left axilla was conducted.

Cetuximab 400 mg/m^2 body surface area (BSA) IV was initiated in June 2019, and the patient subsequently received nine doses of 250 mg/m^2 BSA IV weekly (Fig. 1). Re-staging with cranial magnetic resonance imaging (cMRI) and CT of thorax and abdomen revealed progressive disease (PD) with pleural carcinosis and osseous filiae of the spine in September 2019 (Fig. 3).

After interdisciplinary risk-benefit assessment, cemiplimab 350 mg Q3W was initiated in October 2019 (Fig. 1). The supervising transplant nephrologist discontinued immunosuppressive treatment with tacrolimus and mycophenolate mofetil and gradually reduced methylprednisolone to 2 mg/day. Renal transplant function remained stable under this therapeutic regime.

In January 2020, CT and cMRI follow-up staging revealed complete remission of lung and pleural foci as well as partial remission of osseous metastases. The patient's status remained well under this treatment, and consecutive repetitive radiological follow-up assessments showed stable disease (SD; Figs 1–3). By the end of January 2021, the patient suddenly developed progressive respiratory insufficiency requiring hospital admission in an external hospital. There, she was diagnosed with severe bilateral pneumonia and was treated with intravenous piperacillin/tazobactame. Due to a rapidly declining status, she was transferred to the intensive care unit in the respective hospital. A CT of the thorax showed pneumonitis rather than pneumonia, and thus, high-dose intravenous prednisolone treatment was initiated.

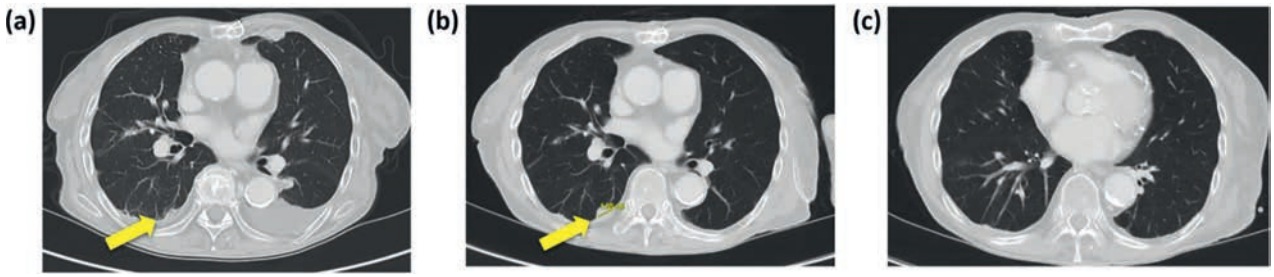

Figure 2 Radiological assessment of pleural metastases. (a–c) Computed tomography images of the thorax are shown. Yellow arrows indicate pleural foci. (a) Identification of pleural foci upon presentation to centre in April 2019. (b) Progressive disease after 3 months of cetuximab treatment in September 2019. (c) Complete radiological remission of foci after 10 months of cemiplimab treatment in August 2020.

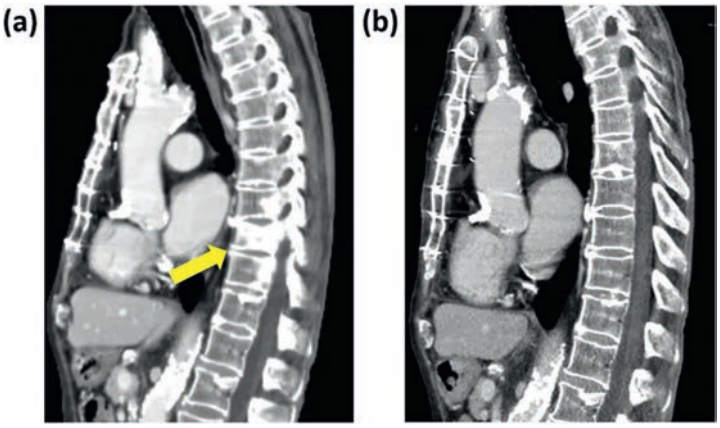

Figure 3 Radiological assessment of osseous metastases. (a, b) Computed tomography images of thorax and abdomen. Yellow arrows indicate osseous metastasis of the spine. (a) Identification of osseous metastases after 3 months of cetuximab treatment in September 2019. (b) Partial remission of osseous metastases after 10 months of cemiplimab treatment in August 2020.

However, the patient quickly became septic and succumbed to multi-organ failure in early February 2021.

Discussion

This case demonstrates the current therapeutic challenge of addressing aggressive metastatic CSCC in a kidney transplant patient. Clinical trials that have led to the approval of immune checkpoint inhibitors, for example cemiplimab, explicitly excluded SOT recipients.[1,2] As studies on the use of ICI treatment in SOT recipients remain sparse, there are currently no clear recommendations for this patient cohort.[3] A recent pooled analysis of published cases of ICI treatment in kidney transplant patients estimated an allograft rejection rate of about 44%, while anti-PD-1 ICI treatment seemed to exhibit a higher risk of transplant rejection compared with anti-CTLA-4 ipilimumab.[4]

For a comparatively reduced risk of transplant rejection compared to ICI, cetuximab was initiated as first-line treatment in the present case. Unfortunately, PD warranted for therapeutic alternatives. Based on an interdisciplinary consensus and after thorough discussion with the patient, cemiplimab treatment was established. Alongside, the supervising transplant nephrologist adapted the concurrent immunosuppressive medication to a minimum required for prevention of organ rejection.

Cemplimab was tolerated well over a period of about 14 months without any signs of organ rejection. Complete remission of the pleural foci occurred after 3 months of treatment. Further progression of the osseous lesions could also be prevented, and some lesions even showed partial remission. Remarkably, the patient reported a significant amelioration of quality of living under cemiplimab treatment.

Only recently, repetitive measurement of quantitative donor-derived cell-free DNA (dd-cfDNA) blood levels has been identified an useful biomarker for detecting allograft injury and rejection among anti-PD-1 ICI treatment in a kidney transplant patients.[5] This promising biomarker should be evaluated in a broader study setting, as it holds a high potential for better monitoring of kidney transplants under ICI treatment. High dd-cfDNA levels may indicate high risk of allograft rejection and could thus help to identify the optimal time point of discontinuation of anti-PD-1 ICI in hopes of retaining the transplanted organ. Alternatively, kidney retransplantation may be a feasible option for selected individuals after allograft rejection under anti-PD-1 ICI treatment.[6] In the presented case, cemiplimab treatment response was promising and did not result in allograft rejection. Had the patient developed rejection, it should be noted that complete remission of metastatic CSCC, specifically of the osseous lesions, had not yet been achieved. The latter would not have qualified the patient as a suitable candidate for kidney retransplantation.

However, transplant rejection is not the only risk to keep in mind. Severe immune-related adverse events are a common, potentially life-threatening, complication of ICI treatment, and SOT recipients are no exception. A recent retrospective analysis of six SOT recipients with metastatic CSCC under cemiplimab treatment has revealed severe adverse events in two cases.[7] Interestingly, one of these cases was severe pneumonitis. Due to the late diagnosis of pneumonitis at the external hospital and a rapidly evolving septic condition with multi-organ failure, our patient's condition could not be stabilized despite intensive care treatment with high-dose glucocorticosteroids. Data on differences in occurrence of adverse events and their severity in SOT recipients compared to non-transplant cohorts are limited and warrant large-scale examination. Investigations in the SOT recipient cohort rather focused on safety and efficacy in respect to transplant rejection rather than adverse events due to ICI treatment so far.[8]

In summary, this report underlines the potential of cemiplimab treatment for progressive metastatic CSCC and suggests its suitability as a second-line treatment option in selected kidney transplant recipients. However, both allograft rejection and rare, but not uncommon severe fatal immune-related adverse events, remain a serious risk. The use of cemiplimab, especially as a first-line regimen, should therefore be critically evaluated and discussed with the respective patient.

Additionally, close collaboration with a transplant nephrologist is indispensable.

Acknowledgements

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CASE REPORT

Advanced cutaneous squamous cell carcinoma of the head in two renal transplanted patients treated with cemiplimab

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Abstract It is well known that organ transplant recipients are prone to develop non-melanoma skin cancers, particularly cutaneous squamous cell carcinoma (cSCC). This is explained by the long-term use of immunosuppressants and thus the decrease of the immunosurveillance that protects from developing malignant tumours. Solid organ transplant recipients (SOTRs) are 65–250 times more likely to develop cSCC compared to the general population (Am J Transplant 2017; 17: 2509). Moreover, in these patients cSCCs follow a more aggressive course. Close follow-up and regular skin check-ups by a dermatologist are, therefore, crucial in the management of these patients. When detected early, cSCC can be easily and effectively treated by a simple excision. However, when advanced, outcomes are poor. Immune checkpoints inhibitors (ICIs) have been recently added to our arsenal and represent a breakthrough, having proved to be effective in achieving long-term responses. We, hereby, present two cases of difficult-to-treat cSCCs in renal transplanted patients.
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Conflict of interest

None declared.

Funding sources

None.

What does this study add?

- Advanced and recalcitrant cSCC of the head and neck region in two renal transplanted patients
- cSCC of the head and neck region is complex as there is high morbidity due to aggressive surgery
- Treatment with immune-checkpoint inhibitors: a multidisciplinary approach is essential in order to find the balance between graft rejection and anti-cancer treatment

Case 1

A 50-year-old man underwent a third deceased donor kidney transplantation in 2013 due to end-stage kidney disease related to primary focal and segmental glomerulosclerosis. He was addressed to the dermatology consultation for the first time in 2009. During follow-up, the patient developed a cSSC on the back of his hand in the first half of 2017. His immunosuppressive therapy consisted of 1750 mg mycophenolate mofetil (MMF), 1 mg tacrolimus (TAC) and 2 mg methylprednisolone daily at the time of diagnosis. In September that same year, he developed a nodular basal cell carcinoma of the scalp, an infiltrating cSCC on his cheek and an infiltrating cSCC on the right temple. A cervical and axillar ultrasound and a CT scan did not show any metastatic lesions. However, 2 months later, a recurrence was seen within the scar of the right temple lesion (lesions' characteristics are depicted in Table 1). The nodule was excised and anatomopathological analysis confirmed cSCC. The excision was complete with negative margins for carcinoma but positive for actinic keratosis.

A year after initial diagnosis 2018, a full body ^{18}F-FDG PET/CT scan showed a hypermetabolic subcutaneous lesion located

Carmen Orte Cano and Tess Van Meerhaeghe are coauthors.

Table 1 All lesions characteristics

	Location	Subtype	Infiltration	Ulceration	Histological differentiation	PNI	Margins after excision
Case 1							
Primary	Right temple	Infiltrating	6 mm	Yes	Mild	No	Negative
Recurrence	Right temple	Infiltrating	4 mm	NR	Good	NR	Clean, AK positive
Case 2							
Primary	Medial canthus right eye	Infiltrating	3 mm	NR	Moderately differentiated	Yes	Positive lateral & deep margins
Recurrence	Medial infra-orbital	Recurrence was diagnosed based on 4-mm punch biopsy. No further excision was done due to the morbidity of the surgery.					

PNI, Perineural Invasion; AK, Actinic Keratosis; NR, Not Reported.

on the right masseter, measuring 17 x 32 mm. Follow-up imaging, 2 weeks later, showed an increase in size (47 x 32 x 25 mm) with the mass reaching the temporomandibular joint but without bone involvement. At that time, the patient refused cytopunction and surgery was carried out to excise the mass (excision of right ear outer canal, tragus and parotidectomy) along with a neck lymph node dissection. The anatomopathological examination showed persistence of cSCC with a 45-mm invasion and positive margins without lymph node involvement (pT3N0, stage III). Clinically, the patient was in poor general health and he reported continuous pain majored during meals, as well as headaches.

After multidisciplinary discussion, a decision was made to start radiotherapy but due to patient's poor compliance only 10 sessions were conducted. The cSCC macroscopically recurred seven months later as nodular metastases in the right temporal region. ^{18}F-FDG PET/CT and MRI showed local relapse (Figs 1,2).

Chemotherapy combining 5-Fluoro uracil (5FU) and carboplatinum was started and his immunosuppressive treatment was reduced to methylprednisolone 8-mg monotherapy. The patient received a total of 2 cycles but was admitted in the emergency department for a haemorrhagic shock due extensive bleeding from the ear, requiring an embolization of the external carotid artery. Evaluation with ^{18}F-FDG PET/CT revealed progressive local disease despite chemotherapy. After a multidisciplinary consult the decision was made to start a treatment with cemiplimab 3 mg/kg every 2 weeks (humanized anti-PD-1 monoclonal antibody). The patient was aware of the risk of graft rejection and agreed on starting therapy.

Re-evaluation of the lesion after 5 administrations of cemiplimab showed a mixed response with almost complete regression of the subcutaneous lesions, but progression of the osteolytic lesion at the skull base. Clinically the patient showed a good response with pain reduction and ulceration of the cutaneous lesions. Because of recurrent infectious episodes, some doses were skipped and consecutive controls showed local progressive disease. His kidney function remained stable during the whole treatment course and there were no signs of graft rejection.

By the end of the year, the progression was clinically evident: The mass had connected with the buccal cavity and the patient presented many episodes of bleeding. Finally, immunotherapy was stopped and palliative care was initiated. In March 2020, he was hospitalized due to a progressive confusional state. He suffered from a pneumocephalus and passed away a few days later.

Case 2

An 80 year-old-man with an IgA nephropathy, for which he was transplanted in 1999, was followed in our dermatology department since 2013. In late 2019, he presented with a nodular erythemato-squamous lesion on the medial canthus of the right eye. The anatomopathological examination after excision showed a moderately differentiated and 3-mm invasive cSCC with perineural invasion. Lateral and deep margins were positive. The immunosuppressive treatment at that time consisted of TAC 1 mg, MMF 250 mg and methylprednisolone 4 mg. The patient was seen again in early 2020, when he presented an erythematous and tense nodule over the operated area. This nodule was considered a recurrence and ^{18}F-FDG PET/CT scan and MRI of the head showed a high hypermetabolic lesion in the infra-orbital region with invasion of the medial wall of the orbit, but without any signs of distant metastases. Multidisciplinary discussion concluded that further surgery could not be performed without major disfiguration and that radiotherapy on that area would lead to major side effects. Immunotherapy was presented as a fair alternative, and so we decided to start treatment with cemiplimab (3 mg/kg, 1 cycle every three weeks). The patient was informed about the risk of graft rejection. TAC and MMF were withdrawn, and methylprednisolone was increased to 8 mg daily. After only 2 cures, a follow-up ^{18}F-FDG PET/CT scan showed a complete metabolic response. After mass reduction, plastic surgeons were able to perform a blepharoplasty, and histology confirmed no signs of malignancy. However, kidney function declined and two kidney biopsies were performed in August and October 2020. Both biopsies showed transplant glomerulopathy with 50% interstitial fibrosis and tubular atrophy, as well as grade 3 chronic arteritis. Immunofluorescence was negative for C4d endothelial staining and screening for

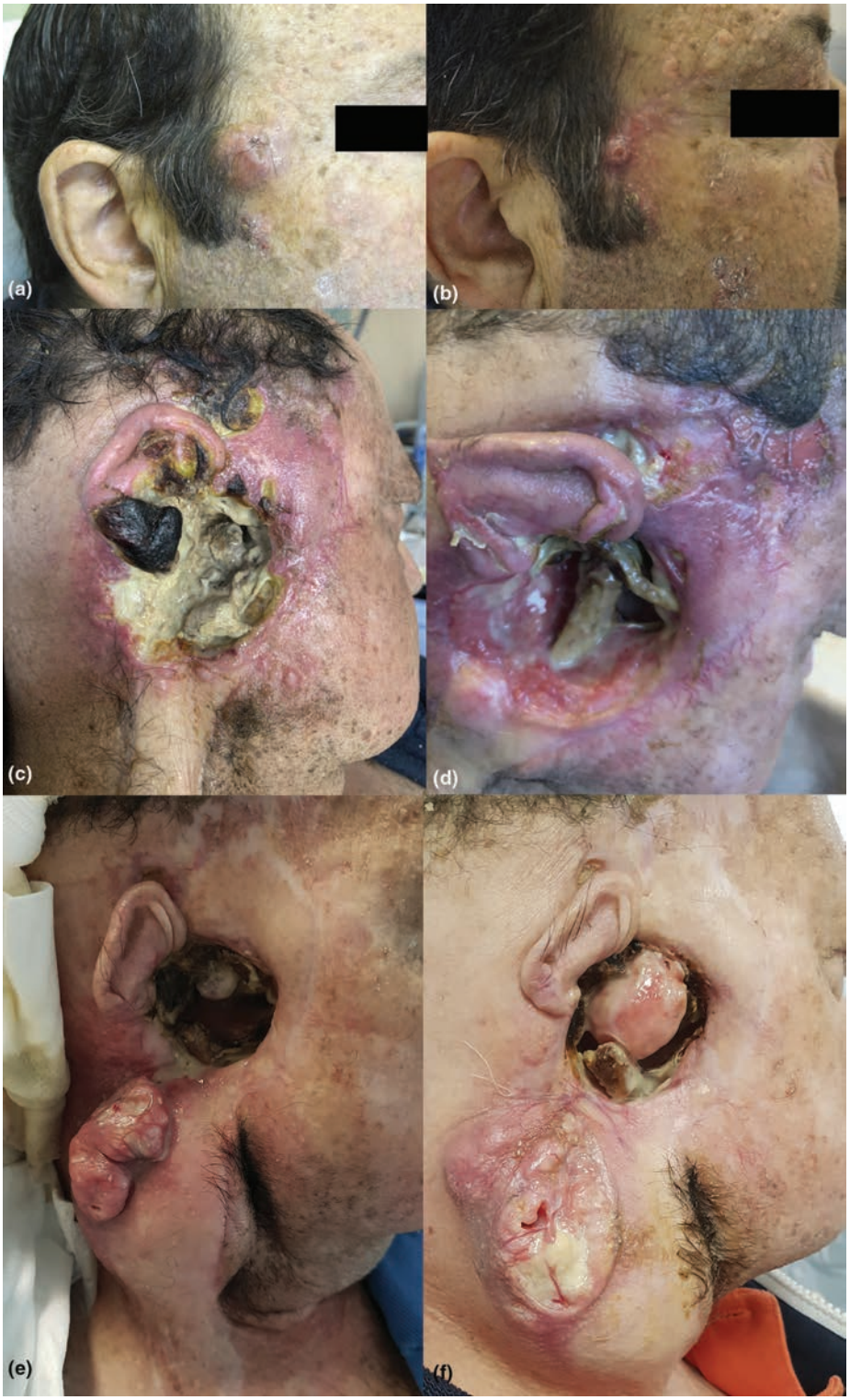

Figure 1 (Case 1) Primary SCC of the right temple presenting as a nodular erythematous lesion (a). Recurrence (b). Disease progression (c). Dissociated response after five cures of cemiplimab (d). Local disease progression and connection with buccal cavity in September 2019 and January 2020 (e, f respectively).

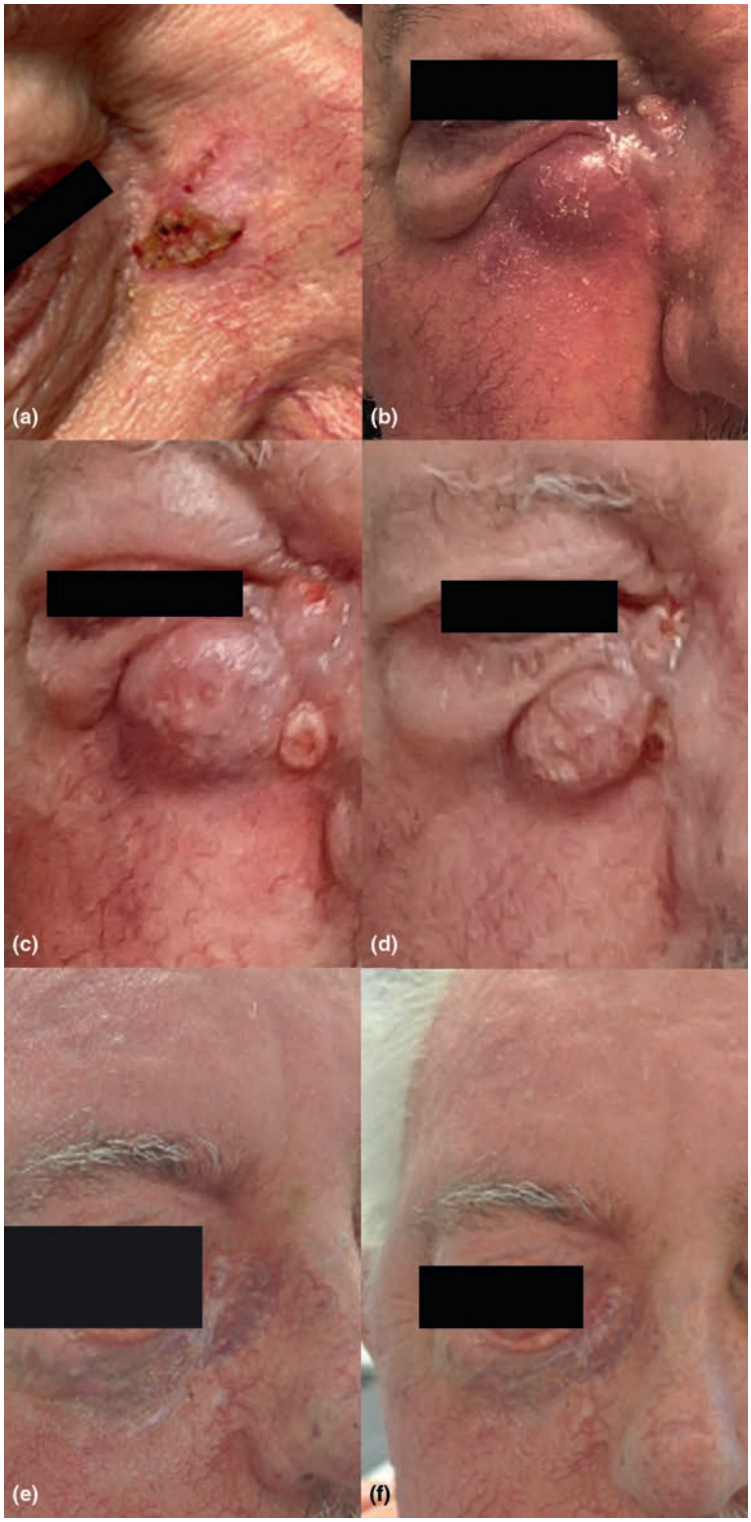

Figure 2 (CASE 2) Ulcerated erythemato-squamous lesion of the interior canthus of the right eye confirmed as primary SCC (a). Tense nodular erythematous lesion confirmed as SCC recurrence, before first dose of cemiplimab (b). One and two weeks after first dose of cemiplimab (respectively, c, d). Results after two doses of cemiplimab and reconstructive surgery (e, f).

donor specific antibodies was negative. Kidney dysfunction was not attributed to anti-PD-1 treatment, but to chronic transplant nephropathy. Consequent ^{18}F-FDG PET/CT scans each show a complete local response with no evidence of metastatic disease. Graft function is still intact and patient's quality of life was preserved.

Discussion

These two cases illustrate the importance of a close dermatological follow-up for prompt diagnosis and rapid intervention of high-risk cSCCs. As patients at risk, OTRs should have regular skin check-ups, ideally in dedicated consultations with a specialized dermatologist. In case 1, the patient's low compliance led to a late diagnosis. Despite the invasive surgery, the cSCC recurred and immunotherapy was only initiated late in the disease course, which led to the disease progression and fatal outcome. In case 2, the patient benefited of immunotherapy early in the disease course and showed a good response. This raises the question about when to initiate immunotherapy in the course of advanced cSCC in patients with a renal graft.[1]

Moreover, special attention should be paid to features associated with progression towards metastatic disease. Both our patients presented with infiltrating cSCCs of the head. This location can be challenging for surgeons, who have to provide the best aesthetic results possible, whilst entirely excising the lesion. What is more, local recurrences have already been reported despite the complete excision with negative margins at histological examination. This could be explained by perineural spread of tumour cells. In fact, perineural invasion has been described as a strong independent predictor of recurrence.[2-4] Surgery of a potentially aggressive cSCC should take this into account and adjuvant radiotherapy should be considered in these cases.

Table 2 resumes the risk factors and their metastatic likelihood as described by Schmults *et al.*[3]

The anti-PD-1 antibody cemiplimab (LIBTAYO®; cemiplimab-rwlc) has proven anti-tumour activity with durable responses in patients with advanced cSCC and was first approved by the FDA in September 2018 for this indication and then in 2019 by the EMA (conditional approval). The therapeutic approach for advanced cSCCs in OTRs is, however, still a dilemma as these patients have been excluded from clinical studies with anti-PD-1 therapy due to potential graft rejection.[5,6] Other systemic options such as chemotherapy (cisplatin, 5FU) and anti-EGFR are available but head-to-head prospective clinical studies are lacking. In addition, radiotherapy has proven good results for localized disease and might also be part of the solution in oligometastatic desease.[7] Especially in OTRs, local therapies should outweight immunotherapy.

Table 2 High-risk factors for lymph node metastases in cSCC

Risk factor	Metastatic likelihood
Size >2 cm	20%–30%
Invasion into subcutaneous fat (depth 5 mm)	16%–45%
Poorly differentiated/undifferentiated grade	12%–32%
Perineural invasion	40%–47%
Lymphovascular invasion	40%
Location near ear or lip	10%–30%
Local recurrence	25%–62%
cSCC in pre-existing scar (burn or trauma)	38%
Immunosuppression	13%–20%

Adapted from Schmults, C, *et al*. JAMA Dermatol 2013; 149: 541.

Tsung *et al*. first published a retrospective study on the use of ICIs in seven SOTRs with metastatic cSCC.[8] They suggest that the use of a prophylactic steroid regimen before and after treatment infusion may prevent immune-related adverse events, including allograft rejection. Another systematic review from Fisher et al., including 57 SOTRs with different cancers treated by ICIs found that most deaths occurred due to progression of metastatic cancer and not following graft rejection. The highest rate of rejection was seen in patients with a kidney transplant (44%), however, the highest rates of death secondary to graft rejection were seen in liver transplant patients (30%). Time from initiation of immunotherapy to graft rejection occurred always within the first two months, with a median of 11 days.[9,10] Concerning adjustments in immunosuppressive therapy, maintaining high immunosuppression could potentially dampen the anti-tumour efficacy of ICIs. On the other hand, lowering immunosuppression before ICI treatment significantly increases the risk of graft rejection.[9-14] Optimal immunosuppressive protocols in these patients are still to be determined. Some data favour mTOR inhibitors over the use of calcineurin inhibitors.[15,16] Several preclinical models have proven anti-cancer benefits of mTOR inhibitors due to paradoxal immunomodulatory properties, especially when combined with immunotherapy.[17] However, their immunosuppressive or immunomodulatory effects seem to depend on dosage and administration schedule, and their application remains to be proven in cancer patients. Thus, the switch to mTOR inhibitors at diagnosis of SCC could be potentially deleterious. In the present case reports, immunosuppressive treatment was reduced with no impact on graft function. Both patients reported a clinical improvement with intact graft function during treatment with cemiplimab. The difference in cancer outcome may be explained by a difference in tumour size, delay in ICI therapy, as well as compliance to treatment. The decision not to instore chemotherapy in the second case may have been life-saving.

Prospective studies on the use of anti-PD-1 therapy in this specific population are needed to identify patients at high risk of rejection and to predict patients resistant to treatment. When confronted with aggressive cSCC, especially of the head and neck region, one must consider quality of life, risk of progression and probability of graft rejection. Today, the risk of rejection is ill-defined and factors predisposing to this life threatening event

are yet to be identified. Treatment choice should be made after discussion with the different specialists involved, as well as with the patient.

As illustrated in the present case reports, early detection and treatment with immunotherapy could be life-saving without graft rejection in this particular setting.

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CASE REPORT

Cutaneous SCC with orbital invasion: case series

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Abstract

Cutaneous squamous cell carcinoma (cSCC) is the most common tumour entity that grows secondarily into the orbital area, while basal cell carcinoma (BCC) is the most common periocular and eyelid tumour. Diagnostic delays are common and may increase post-treatment complications. The therapy is challenging and must be discussed at an interdisciplinary tumour board. We discuss four cases of cSCC with orbital invasion treated with immune-checkpoint inhibitors with variable responses.

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Conflict of interest

Mirjam Nägeli has intermittent project focused consulting and/or advisory relationships or/and travel-congress support with Sanofi and SunPharma outside the submitted work. Prof. Dummer has intermittent project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome outside the submitted work. Johanna Mangana has intermittent, project focused consulting and/or advisory relationships with Merck-Pfizer, MSD, Novartis, Sanofi, Pierre Fabre, Amgen and BMS outside of submitted work. She reports also travel-congress support from Loreal, MSD, Ultrasun, BMS and Pierre Fabre. Karla Chaloupka has no conflict of interest.

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What does this study add?

- cSCC is the most common tumour entity that grows secondarily into the orbital area
- Diagnosis often may be delayed due to vague complaints
- Numbness and pain were the most common symptoms
- A rapid response rate is usually seen with anti-PD1 therapy

Introduction

Cutaneous squamous cell carcinoma is the second most common periocular and eyelid cutaneous malignancy, but SCC (including starting from the paranasal sinus) is the most common tumour entity that grows secondarily into the orbital area,[1–3] and perineural orbital invasion of cSCC is a well-described phenomenon, usually occurring along the supraorbital or infraorbital nerves.[4,5] The incidence of perineural spread is about 2.5%–14%.[5] Over 60% of patients with perineural spread may be initially asymptomatic,[6] and diagnosis may be delayed either due to vague complaints or due to significant lag of several years between initial removal of the cSCC and perineural invasion, and the patients may simply not recall having had cutaneous cancer.[5,7,8] If local therapy with surgery, radiotherapy or combination is no more possible or inadequate, systemic medications are indicated in order to achieve adequate tumour control or cure.

We describe four cases of orbital invasion with partly also strongly delayed diagnosis.

Cases

Patient Nr. 1

71-year-old male patient with cutaneous carcinogenesis while taking azathioprine for many years for Crohn's disease showed a rapidly growing nodule in the right medial eyebrow area in February 2020. One year earlier, a proliferating epidermoid cyst had been removed at this site. MR in April 2020 showed extension in the orbital area along the superior rectal muscle

and palpebral levator muscle to the superior orbital fissure. Clinically, he suffered from foreign body sensation and watery eye. Biopsy was compatible with squamous cell carcinoma. The interdisciplinary tumour board advised against mutilating surgery and systemic therapy with anti-PD1 (programmed-cell death protein1) cemiplimab. After 4 cycles of 350 mg each every 3 weeks (May-June 2020), the lesion unfortunately progressed. The patient tolerated the immunotherapy very well except for immune-related agranulocytosis. Molecular analysis with FoundationOneCDx (FOne®CDx) of the tumour detected a tumour mutational burden (TMB) of 38 muts/mb and ERBB2 amplification. FOne®CDx is an FDA-approved 'next-generation sequencing'-based test that identifies genomic alterations in over 300 cancer-related genes. Therefore, an immune histochemical staining of the tumour was performed, which could further confirm the findings of ERBB2 amplification (score of 3+), so that a therapy with trastuzumab (herceptin®) was also recommended in the molecular tumour board. We treated with trastuzumab combined with radiotherapy, which showed a stabilization over 7 months; then, unfortunately the tumour was progressive, so we switched to chemotherapy with carboplatin/paclitaxel in March 2021. In May, he had the 3rd cycle (Table 1 and Fig. 1).

Patient Nr. 2

In 2013, the 76-year-old male patient underwent excision of multiple poorly differentiated cSCCs on the right forehead. In 2017, he developed severe orbital and trigeminal right pain with diplopia. At that point, there was no radiologic correlation to the symptoms by MRI, ultrasound and PET-CT. Lumbar punction was unremarkable and likewise inconspicuous PET-CT in January 2018. The patient presented a right facial palsy in May 2018. Diagnostic work up with MRI revealed a mass in the right orbital area, sinus cavernosus and fossa pterygopalatina and masticator space. The biopsy showed a squamous cell carcinoma. A photon irradiation of the right orbital area was started, which was prematurely terminated due to severe pain (11 cycles). In January 2019, MRI showed progression, with irritation of the trigeminal nerve with clinically severe trigeminal pain. Therapy with anti-PD1 cemiplimab 350 mg flat dose every 3 weeks was begun in March 2019. Three-month surveillance with MRI showed a slow tumour response with only inactive tumour portions/scarring. He had no reported adverse events under this immunotherapy. The patient stopped the therapy after more than 1 year in June 2020 suffering from severe intermittent pain, which limited his quality of life so much that he decide to suicide via Exit organization (Association for humane dying, which support if people decide at some point to exercise your right to self-determination, www.exit.ch).

Patient Nr. 3

76-year-old male patient with previous excision of cSCC in the left temporal area in 2013, presented 5 years later in June 2018 with subcutaneous soft-tissue metastasis at the inner–upper orbital angle on the left. A biopsy could detect a cSCC, R1-resection was performed and postoperative radiotherapy until November 2018 started. In May 2019, PET-CT and MRI showed an intraorbital recurrence with ingrowth into the cavernous sinus as well as protrusion bulbi and optic nerve compression. Clinically, he had an incomplete lid closure, supraorbital pain and exophthalmus. Chemotherapy with carboplatin/paclitaxel in July/August 2019 was given with tumour progression in PET-CT in September. Therapy was changed to anti-PD1 therapy with cemiplimab 350mg flat dose every 3 weeks. TMB showed 63 muts/mb (FOne®CDx). In August 2020, the intraorbital tumour showed a complete response (CR), so therapy was stopped 6 months beyond CR in March 2021. He had no reported adverse events under this immunotherapy, but development of culture-negative lymph node tuberculosis supraclavicular. Clinically, there was complete regression of his exophthalmos and pain.

Table 1 Four patient cases with orbital metastatic cutaneous squamous cell carcinoma

Pat (sex, age)	Risk factors	Location primary cSCC, year of discovery orbital metastasis, treatment	Therapy anti-PD1 duration, response
1 (m, 71y)	IS with azathioprine	Eyebrow right 2/2020, orbital metastasis 4/2020, anti-PD1 (4x), RT, trastuzumab (10x), carboplatin/paclitaxel ongoing	PD (after 3mt)
2 (m, 76y)	None	Frontal right 2013, orbital metastasis 5/2018, photon irradiation, anti-PD1 3/2019-6/2020 (21x)	PR
3 (m, 76y)	None	Temporal left 2013, orbital metastasis 6/2018, surgery and RT till 11/2018, intraorbital metastasis 5/2019, carboplatin/taxol till 8/2019, anti-PD1 9/2019-3/2021 (26x)	CR (after 11 mt)
4 (f, 94y)	None (advanced age)	Frontal median SCC12/2019 not therapy (misdiagnosed as AV malformation), orbital metastasis 5/2020, anti-PD1 6/2020-6/2021	CR (after 6 mt)

CSCC, cutaneous squamous cell carcinoma; RT, radiotherapy; PD, progressive disease; PR, partial response; CR, complete response; IS, immunosuppression.

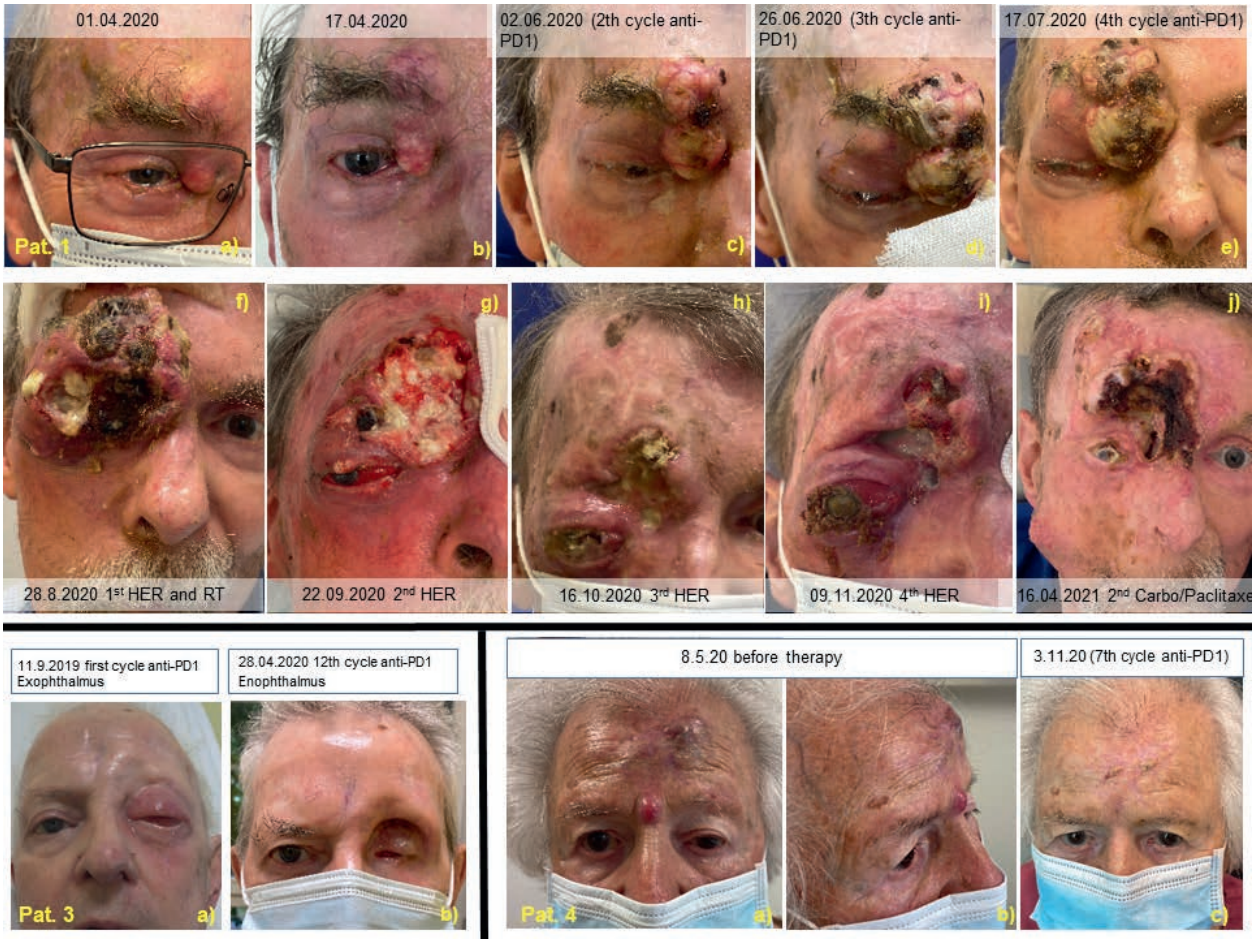

Figure 1 Patient 1) (a-b) before therapy, (c) second-cycle anti-PD1, (d) third-cycle anti-PD1, (e) fourth-cycle anti-PD1, (f) first-cycle trastuzumab (HER: herceptin ®) and start radiotherapy, (g) second-cycle trastuzumab, (h) third-cycle trastuzumab, (i) fourth-cycle trastuzumab, (j) second-cycle carboplatin/paclitaxel. Patient 3) (a) before therapy with exophthalmus, (b) after 11-cycle anti-PD1 with CR and enophthalmus. Patient 4) (a-b) before therapy with ptosis, (c) after 6 cycles anti-PD1 without ptosis and CR.

Patient Nr. 4

94-year-old female patient present with a mass on the forehead left since at least December 2019. It was assessed as an AV malformation on CT. No cSCC was pre-described. In May 2020, a new nodule appeared at the glabella with the development of ptosis on the left with numbness at the forehead left. Biopsy of this nodule showed a poorly differentiated cSCC. MR showed a hypervascularized tumour on the left mid-supraorbital forehead that grew intraorbitally to the apex of the orbit and infiltrated the cavernous sinus. A therapy with anti-PD1 cemiplimab was decided (high risk of visual loss with radiotherapy), which was started in June 2020 with 350 mg flat dose every 3 weeks. Clinically and radiologically, the patient showed a rapid response with CR in December 2020, so that treatment cessation is planned for June 2021. She had no reported adverse events under this immunotherapy.

Discussion

Treatment of orbital lesions with deep perineural invasion (PNI) is challenging, and excessive surgery including a disfiguring exenteration at that stage is in vain. Early diagnosis and uncompromised treatment of PNI before entering the orbital area are crucial for the survival of the patient. Histologic detection of PNI can be difficult on routine sampling, and neural involvement is often not addressed in pathology reports.[6] Numbness and pain were the most common symptoms, whereas ophthalmoplegia, ptosis and facial palsy were the most frequent signs.[8] As an initial symptom, patient 1 suffered from foreign body sensation, patient 2 had severe orbital and trigeminal pain with diplopia, patient 3 had an incomplete lid closure, supraorbital pain and exophthalmus and patient 4 showed ptosis and numbness. Missing the early primary treatment of an extraorbital PNI will cause a hidden

spreading. At that stage, MRI imaging might not show the perineural invasion and, therefore, not guide to a targeted biopsy until it is too late.

Wide surgical excision alone or in combination with radiotherapy is the primary treatment of choice before the perineural invasion enters the orbit. The number of orbital exenterations due to carcinoma differs in the literature with SCC being the largest subgroup.[9] In most cases, recurrence occurs within the first 2 years, despite exenteration.[10] Promising results compared with previous local and systemic treatment options such as radiotherapy, chemotherapy, radiochemotherapy or antibody therapy with an EGFR inhibitor are currently seen with anti-PD1 as a newly approved first-line therapy.[11,12] A rapid response rate is usually seen with anti-PD1 therapy. The metastatic cSCC group showed an objective response in 47% of patients with emerging evidence of durable response and disease control.[13]

This therapy leads to an improvement in quality of life, which is often very poor in advanced or metastatic cSCC, as seen in patient number 2.[14] The management of patients with cSCC in high-risk locations such as periorbital area is demanding and integrates various disciplines. Interdisciplinary case discussion for treatment planning is of utmost importance in these cases. This includes dermatologists, dermatooncologists, oncologists, ophthalmologists, radiologists, pathologists, radiooncologists, surgeons from various specialties and psychologists.

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The patients in this manuscript have given written informed consent to the publication of their case details.

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CASE REPORT

Aggressive cutaneous squamous cell carcinoma in a hydroxyurea- and ruxolitinib-pretreated patient with polycythaemia vera

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Abstract Hydroxyurea and ruxolitinib are frequently used to treat myeloproliferative disorders, including polycythaemia vera, and chronic treatment is associated with many cutaneous adverse effects such as the development of aggressive non-melanoma skin cancer (NMSC). We report an 85-year-old man with a history of hydroxyurea- and ruxolitinib-treated polycythaemia vera who was referred for the management of progressively growing tumours on his scalp. Histopathology of the largest scalp lesion revealed a partly desmoplastic cutaneous squamous carcinoma with perineural invasion. Initial imaging revealed metastatic disease in cervical lymph nodes, bones and lungs. The scalp lesions were successfully treated with bleomycin-based electrochemotherapy. Under initial systemic therapy using four cycles of cetuximab, metastatic disease progressed. Following the approval by the health insurance, compassionate use of pembrolizumab monotherapy was initiated. After three cycles of pembrolizumab, however, metastatic disease further progressed and the patient finally died from global respiratory insufficiency. The present case exemplifies the cutaneous adverse effects of long-term hydroxyurea and ruxolitinib therapy, frequently resulting in highly aggressive NMSCs that are usually not responsive to systemic treatments even such as immune checkpoint inhibitors.
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Conflict of interest
None declared.

Funding source
None.

What does this study add?
Long-term hydroxyurea and/or ruxolitinib therapy frequently results in the development of highly aggressive non-melanoma skin cancers that are often not responsive to systemic treatments even such as PD-1 blockers.

Introduction
An increased occurrence of non-melanoma skin cancer (NMSC), such as cutaneous squamous cell carcinoma (cSCC), has not only been described following the long-term treatment with the anti-metabolite hydroxyurea (HU) but also under Janus kinase 1 and 2 inhibitors (JAKi) therapy for haematological malignancies. It has been reported that NMSC developing in patients on ruxolitinib therapy exhibit a more aggressive and metastatic profile.[1–6] We report a polycythaemia vera (PV) and long-term HU and ruxolitinib therapy who developed highly aggressive cSCC not responding to cetuximab and pembrolizumab treatment.

Case presentation
An 85-year-old man with a 9-year history of PV and renal insufficiency was referred to our skin cancer centre for the management of progressively growing lumps on his scalp. His PV had previously been treated with HU over 3 years. Thereafter, his medication was switched to ruxolitinib 15–0–20 mg/day. On examination, there was a huge ulcerated tumour on the head in the parietal region (Fig. 1). Moreover, there were multiple smaller nodules in the temporal and occipital region. Histopathology of a scalp lesion revealed a partly desmoplastic cSCC with perineural invasion (Fig. 1). PET-CT revealed multifocal metastatic disease, including several tumours frontoparietal and occipital, bilateral cervical lymph node metastases, and pulmonal and skeletal metastases in thoracic spines. Lactate dehydrogenase and blood lymphocytes were within the normal range at baseline. We treated the cutaneous lesions on the scalp with standard

bleomycin-based electrochemotherapy under general sedation resulting in clinical resolution of almost all exophytic tumours treated.[7] Since anti-PD-1 agents were not approved for metastatic cSCC at this time, systemic therapy was initially performed using cetuximab infusions with 400 mg/m^2 body surface.[8] Four cetuximab cycles were weekly administered until the patient's insurance approved the compassionate use of pembrolizumab. At this time, his metastatic disease was progressive, including the occurrence of new liver metastases. Pembrolizumab (2 mg/Kg per body weight) was administered for 3 weeks. About three weeks after the third pembrolizumab cycle, the patient attended our department in significantly reduced condition. Imaging demonstrated multifocal progressive disease. One day after admission, he died from global respiratory insufficiency.

Discussion

Advanced cSCC is a life-threatening condition, in particular for patients not eligible for curative surgery or radiation. Recently, a novel treatment approach with the immune checkpoint inhibitor (ICI) cemiplimab, a potent monoclonal antibody directed against programmed death 1 protein (PD-1) receptor, has been approved as single agent for the treatment of adult patients with metastatic or locally advanced cSCC who are not candidate for curative surgery or radiotherapy. Migden *et al*.[9] reported consistent response rates in phase I and II studies of patients with advanced cSCC managed with cemiplimab. These data suggest that cases with advanced cSCC, ineligible for an intensive approach, such as platin-based chemotherapy regimens, may respond to ICIs such as cemiplimab, which has shown an important anti-tumour activity and an acceptable safety profile with adverse events that are similar to those seen with other PD-1 blockers used for the treatment of other malignancies.[9] In patients with advanced cSCC, positive efficacy and safety data were also reported for other PD-1 blockers such as pembrolizumab and nivolumab.[8,10,11]

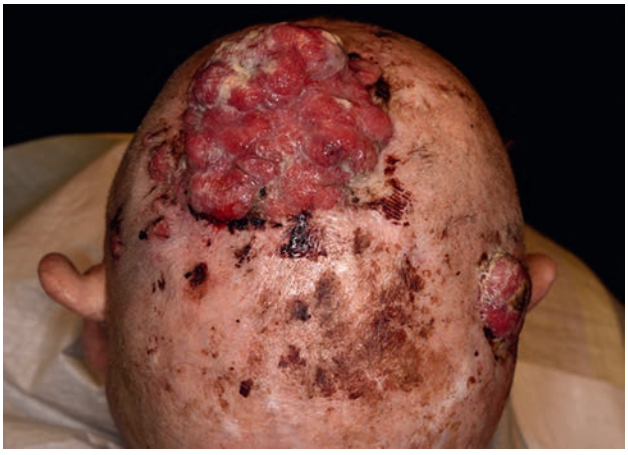

Figure 1 A large ulcerated cutaneous squamous cell carcinoma on the parietal region of a hydroxyurea- and ruxolitinib-pretreated patient with polycythaemia vera. A smaller metastatic nodule is also seen on the left temporal region.

Our elderly patient with PV developed cSCC during treatment with ruxolitinib, but he had also been treated over 3 years with HU. Hence, an iatrogenic pathogenesis is likely as the cause of the aggressive cSCC observed. The high prevalence and fatality of skin cancers in patients with concomitant haematological neoplasms has been mainly attributed to an impaired immune function, which is particularly true for patients with chronic lymphatic leukaemia (CLL). Impaired B-cell function and functional defects of T-cell subsets and increased T regulatory cell activity, may result in CLL patients to secondary skin malignancies. In patients with PV, however, the immunosuppressive effects resulting from the treatment of the haematological malignancy might crucially contribute to the immunocompromised state in PV patients. Gomez *et al*.[12] recently demonstrated that the risk to develop cSCC in PV patients results from the combined effect of common risk factors (age, male sex) together with cytoreductive treatments such as HU. Notably, Leiter *et al*.[13] showed that compared to patients without haematological malignancies, the observed treatment outcome of ICIs was significantly reduced in cSCC patients regarding progression-free survival, but not in melanoma and Merkel cell carcinoma patients.[13]

Interestingly, few data are available on the co-administration of ruxolitinib and anti-PD-1/PD-L1-based ICI. Debureauxet *et al*.[14] reported a promising effect of the association between ruxolitinib and nivolumab in a patient with essential thrombocythaemia and advanced Merkel cell carcinoma who achieved a complete response after four cycles of nivolumab. Based on the strong response observed, the authors hypothesized that the PD-1/PDL-1 pathway and JAKi could constitute complementary therapeutic targets and that the combination of nivolumab and ruxolitinib might be synergistic, despite a T-cell depletion often caused by JAKi that could result in a potential loss of efficacy of ICI treatment. In the present case, the JAKi was continued during anti-cSCC management. However, we did not observe any synergistic positive effect between ICI treatment and anti-JAKi with respect to cSCC control.

In conclusion, the present case exemplifies the cutaneous adverse effects of long-term HU and ruxolitinib therapy, frequently resulting in highly aggressive metastatic cSCC that are usually not responsive to systemic treatments even such as ICIs. Due to the increased risk of NMSC among patients on HU and/or ruxolitinib treatment with haematological malignancies, regular routine skin examinations are mandatory in this population.

Acknowledgement

The patient in this manuscript has given written informed consent to the publication of his case details.

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CASE REPORT

Complete response of advanced cutaneous squamous cell and basal cell carcinomas with sequential cemiplimab and sonidegib therapy

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Abstract A 78-year-old woman was referred to our skin cancer centre with three previous incomplete resections in the left cavum conchae of a deep-infiltrating locally advanced, but still asymptomatic basal cell carcinoma (BCC). The patient noted furthermore two rapidly growing exophytic lesions in the left preauricular and cervical area in the last weeks. The clinical and histological distinction of locally advanced from metastatic cutaneous squamous cell carcinoma (CSCC) lesions was challenging. Imaging analysis with CT scans showed, however, an involvement of the parotid gland as well as multiple small lymph node metastases. The interdisciplinary tumour board decision at our institution recommended a systemic treatment with the PD1-antibody cemiplimab. After 13 cycles with cemiplimab at a dose of 350 mg intravenously every 3-weeks, the patient showed a complete response of the two CSCC lesions with histological confirmation. However, the BCC of the left ear appeared to be unchanged and still asymptomatic. The interdisciplinary tumour board considered this tumour to be no candidate for a curative resection or irradiation. Therefore, the patient was exposed to the hedgehog inhibitor sonidegib with a conventional dose of 200 mg orally per day. After 3 months of treatment, the tumour showed a markable regression and a complete response was confirmed by 3-punch biopsies from this preoperated lesion. Both cemiplimab and sonidegib were excellently tolerated with almost no adverse events apart from a mild fatigue (CTC grade 1) over the first 3 weeks of the cemiplimab therapy. There were no laboratory abnormalities found.
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Conflict of interest

AH reports grants and personal fees from Amgen, grants and personal fees from BMS, grants and personal fees from Eisai, grants and personal fees from Immunocore, grants and personal fees from MerckPfizer, grants and personal fees from MSD/Merck, grants and personal fees from Novartis Pharma, grants and personal fees from Philogen, grants and personal fees from Pierre Fabre, grants and personal fees from Regeneron, grants and personal fees from Replimune, grants and personal fees from Roche, grants and personal fees from Sanofi-Genzyme, grants and personal fees from Seagen outside the submitted work. MW has received grants or contracts by MSD and Millennium, consulting fees by Sanofi, MSD, BMS, Novartis, Sun Pharma, payment or honoraria for lectures from Medac, support for attending meetings/Travel by Novartis, Pierre Fabre, MSD, and is a participant on the advisory board/Data safety Monitoring board of Roche, MSD, Novartis outside the submitted work. CG reports grants from BMS, grants and personal fees from MSD/Merck, grants from Philogen, grants from Regeneron outside the submitted work. JW reports grants and personal fees from MSD/Merck, grants from Philogen, grants and others from Pierre Fabre, grants from Regeneron, grants from Sanofi-Genzyme, personal fees from BMS, outside the submitted work.

Funding source

None.

What does this study add?

- Both basal cell carcinoma and cutaneous squamous cell carcinoma are known to carry a high mutational tumour burden due to UV radiation making them prone to treatment with checkpoint inhibition. However, as shown in this case, the discordant response may be seen even in close vicinity presumably due to a variable degree of neoantigen expression.

Introduction

The treatment of metastatic and locally advanced cutaneous squamous cell carcinoma (CSCC) was extremely difficult in the era of chemotherapy and EGFR receptor inhibitors like cetuximab. Response rates were relatively low and the duration of response short. Since 2019 immunotherapies with PD-1 antibodies are the new standard of care.[1–3] The EADO guideline 2020 highlights cemiplimab as the only approved immune checkpoint inhibitor for locally advanced and metastatic CSCC, which are no good candidates for curative surgery or irradiation. Very recently, Stratigos *et al.*[4] showed the first data on a new clinical trial (REGN-1620) on cemiplimab in previously treated locally advanced and metastatic basal cell carcinomas (BCC) patients, who were either refractory or intolerant to the approved sonic hedgehog inhibitors vismodegib or sonidegib. A promising response rate of 28% with a high rate of durable responses (85%) after 1 year of follow-up has been demonstrated.

Both epithelial skin cancers (CSCC and BCC) are known to develop on sun-damaged skin and are going along with a high tumour mutational burden (TMB)[5]. Previously, it has been shown that these skin tumours are particularly sensitive to immune checkpoint inhibitors like the PD-1 antibodies.[6,7]

Case description

In autumn 2019, a 78-year-old fair-skinned woman presented in our outpatient clinic with two rapidly growing exophytic lesions in the left preauricular and cervical areas. Clinically and histologically the lesion on the mandibula was considered as a primary tumour, whereas the lesion next to the ear appeared as a metastasis from this primary CSCC. A CT scan showed that the metastasis infiltrated not only the local skin, but also the parotid gland. Furthermore, multiple lymph node metastases of the neck with a maximum diameter of 1cm have been detected in the scan.

Our patient had a medical history of three incomplete resections of a deep infiltrating locally advanced BCC in the left cavum conchae by an ENT surgeon. The last surgery was 2 weeks before the patient was referred to our skin cancer centre. A clinical and dermatoscopic evaluation in our unit could not clearly distinguish between scarring or fibrosis and an active BCC, but multiple punch biopsies confirmed the diagnosis of an aggressive BCC.

The further medical history of our patient was unsuspicious with the exception of a long-known hypercholesterinaemia and a mild arterial hypertension. The patient had no other comorbidities.

Two months later, our interdisciplinary tumour board discussed the patient and considered her not as a good candidate for curative surgery or irradiation (Fig. 1a). There was a consensus for a systemic treatment with the PD1-antibody cemiplimab approved for this indication (CSCC). The treatment was initiated with the approved dose of 350 mg i.v. every 3 weeks. After one infusion, there was already a marked decrease in the size of the two CSCC lesions and they became necrotic. Furthermore, there was a flare-up of pre-existing actinic keratoses in the UV-damaged skin of the face and neck (Fig. 1b). We continued the treatment till August 2020, when the patient clinically showed a complete response of the SCC lesions after 13 cycles with cemiplimab. In both CSCC areas control biopsies revealed no active tumour cells, but only fibrosis. We considered these findings as a histologically proven complete response (CR) with an excellent cosmetic outcome (Fig. 1c).

However, the BCC on the left cavum conchae appeared to be widely unchanged during the treatment with cemiplimab (Fig. 2a). A biopsy showed remaining BCC with an aggressive histotype, and therefore, the patient was again discussed in the interdisciplinary tumour board. Here, the surgeons considered our patient now as before still as no candidate for a surgical intervention and the radiotherapists refrained from an irradiation, too. Now, in September 2020, the treatment recommendation was to stop cemiplimab due to the CR and initiate a treatment with the hedgehog inhibitor sonidegib at the approved dose of 200 mg orally per day. At her last visit in January 2021, the BCC appeared to be significantly smaller and still asymptomatic, but we were uncertain with the naked eye and dermoscopy evaluations if this is a complete response (Fig. 2b). Therefore, three-punch biopsies from the most suspicious areas of the heavily pretreated BCC have been taken and histologically evaluated. Consistently they showed only fibrosis and no BCC tumour cells. Both CSCC lesions were still in CR.

It needs to be mentioned that both treatments were very well tolerated in our elderly patient. During the cemiplimab applications, only a mild fatigue syndrome (CTC grade 1) in the first weeks was noted. During the sonidegib treatment, our patient had absolutely no adverse events despite the well-known and frequently observed side effects in other patients. Our patient had no impairment in the quality of life. In the absence of significant toxicities and laboratory abnormalities, we continued the treatment with sonidegib for another 3 months until April 2021 to maintain the impressive response.

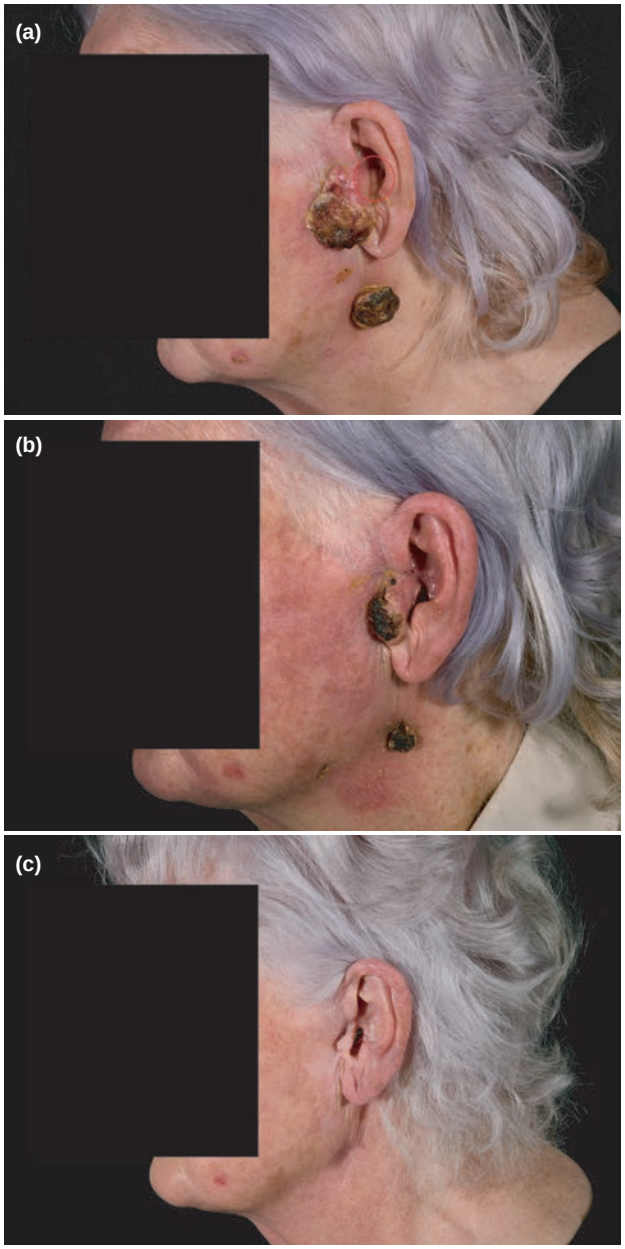

Figure 1 (a) Cutaneous squamous cell carcinoma (CSCC) and basal cell carcinoma (BCC; red circle) lesions before treatment (November 2019). (b) CSCC and BCC lesions after just 1 cycle with cemiplimab (December 2019). (c) Complete response of the CSCC after 13 cycles of cemiplimab (August 2020).

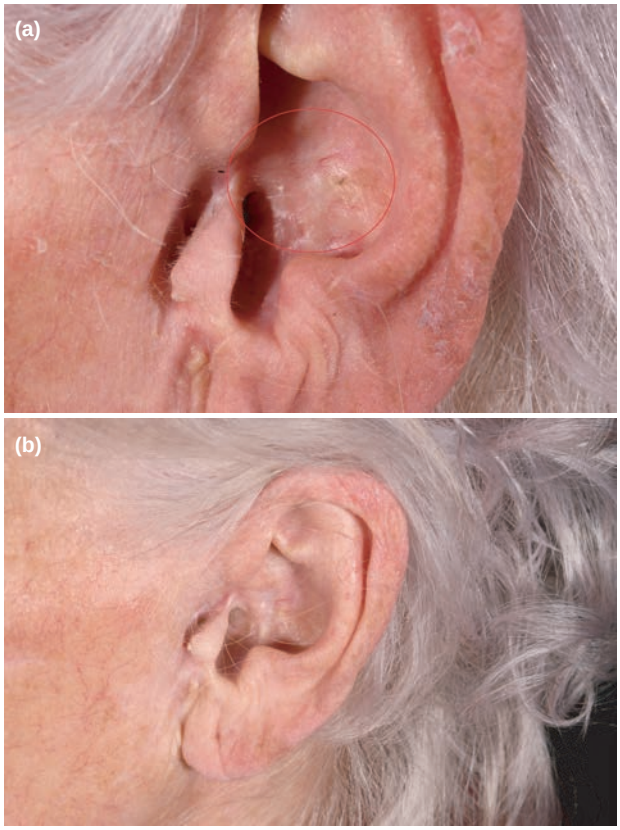

Figure 2 (a) Basal cell carcinomas (BCC; red circle) of the cavum conchae, pretreatment (September 2019). (b) Histologically confirmed CR after sonidegib treatment (January 2021).

Discussion

Clinically and histologically it was hard to distinguish locally advanced from metastatic CSCC in this particular patient. The clinical and histological features of the preauricular lesion led us to believe that this lesion was a metastasis, which also invaded the parotid gland. The decision to treat this patient systemically was based on the approval of cemiplimab for locally advanced and metastatic CSCC as well as the first report of a successful treatment with the same drug in locally advanced BCC. Overall, the patient needs to be considered as a mixed responder, since the CSCC lesions regressed completely (complete response, CR), whereas the locally advanced BCC remained stable (stable disease, SD) during cemiplimab treatment. The discordance of the treatment response to the PD-1 antibody is still unclear, but however discrepant values for the PD-L1 expression on the tumour surfaces and different tumour mutational burden (TMB) may play a role. Whereas for the CSCCs the role of UV damage is considered as the main carcinogen, UV-light may not be the driving cause of a BCC in the cavum conchae and thus the TMB is probably much lower. The subsequent treatment with sonidegib as a hedgehog inhibitor approved for this particular disease led to a complete response. Our sequential approach shows that the therapeutic repertoire provides a good chance for patients with locally advanced non-melanoma skin cancer (NMSC) to benefit without an impairment in the quality of life.

In our experience, there are no upper age limits to use these drugs for skin cancer and very few patients have clear contraindications. This case is of particular interest since it allows distinct observations on cemiplimab treatment simultaneously occurring in CSCC and BCC with varying responses.

Acknowledgement

The patient in this manuscript has given written informed consent to the publication of her case details.

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CASE REPORT

PD-1 inhibitor therapy of basal cell carcinoma with pulmonary metastasis

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Abstract Basal cell carcinoma (BCC) may be challenging to differentiate from basaloid squamous cell carcinoma (bSCC), both clinically and histologically. BCC constitutes one of the most common tumours and metastatic behaviour is extremely rare. In contrast, bSCC is a rare entity with an increased propensity for distant metastasis. If these conditions develop into inoperable metastatic disease, the therapeutic alternatives are different, but the use of PD-1 inhibitors may be a valid option for both. Here, we report a case with complex histology with a component initially classified as bSCC with lung metastases and treated with the PD-1 inhibitor cemiplimab resulting in radiological and clinical responses. Re-examination of the lung biopsy using routine histomorphology in combination with immunohistochemical staining for cytokeratin 14, cytokeratin17 and BerEp4 has, however, revealed a histopathological pattern of BCC, which is in concordance with a similar analysis of the cutaneous primary tumour in the face that the patient underwent surgery for more than 5 years earlier.
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Conflicts of interest

IJ, none; ML, Honoraria for lectures (Bristol Myers Squibb, MSD and Roche); LMA, none; ROB, Research grants (Bristol Myers Squibb , SkyLineDx, Inst.), Honoraria for lectures (Roche, Pfizer), Advisory Boards (Amgen, BD/BARD, Bristol Myers Squibb, MSD, Novartis, Roche, Sanofi Genzyme); LN, Research grants (Merck, Syndax Pharmaceuticals, Inst.), Honoraria for lectures (Pfizer, LeoPharma, Bristol Myers Squibb, MSD, Novartis), Advisory Boards (Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Sanofi Genzyme)

Funding sources

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What does this study add?

- Metastatic basal cell carcinoma (BCC) is responsive to PD-1 inhibitor therapy.
- Immunohistochemical staining against cytokeratin 14 and 17 may be helpful in tumours with overlapping histology, discriminating BCC from basaloid squamous cell carcinoma (bSCC), which subsequently may be of importance in the selection of systemic therapy if metastatic disease occurs.

Case report

A 66-year-old Caucasian man was admitted to the Dermatology and Pulmonary Medicine departments for further examination. In the past, the patient had undergone extensive and 10-fold repeated surgery due to a locally advanced basal cell carcinoma (BCC) of morpheiform infiltrative type that engaged the skin of the left chin, with extension to the mucosa and bone tissue of the maxillary sinus. Recent follow-up examinations after surgery, which included clinical examinations, repeated biopsies and radiology, had not demonstrated any signs of local relapse of

disease. However, following a fall accident where he hurt himself badly, he was admitted for an acute CT scan that demonstrated tumour-like lesions in the left lung and a thickening of the pleura at the same side. Dermatological examination did not reveal any malignant skin lesions, but an FDG PET-CT scan confirmed the CT scan with FDG uptake in tumour-like lesions in the left upper lung lobe and pleura. The patient underwent biopsy of the pleural lesion where the pathology report described a basaloid epithelial tumour consistent with basaloid squamous cell carcinoma (bSCC), where primary or metastatic bSCC and BCC were included in the differential diagnosis. On clinical examination, no primary bSCC was identified in the usual primary tumour sites.

Subsequently, the patient initiated therapy with the hedgehog inhibitor vismodegib that resulted in a radiological partial response. Following 14 months of treatment with vismodegib, a new FDG PET-CT scan was performed that revealed residual disease with FDG uptake, especially in the lymph nodes of the left lung hili and the left upper lobe (Fig. 1). In parallel, the patient suffered from severe toxicity associated with the vismodegib treatment. He had lost almost 20 kg in bodyweight, suffered from fatigue, grade-3 diarrhoea, abdominal pain and decreased appetite. Considering the challenging clinical situation the patient was evaluated and included in the Early Access programme for the PD-1 inhibitor cemiplimab, that is, treatment with cemiplimab 350 mg IV every third week. After 3 months of therapy, a new FDG PET-CT scan was conducted, which demonstrated a partial remission with reduced FDG uptake that also was associated with an improved performance status with loss of abdominal pain, decreased diarrhoea and a weight gain of almost 10 kg. The patient then completed additional 9 months of cemiplimab therapy until the Early Access programme was closed. At this stage, repeated regular CT scans and FDG PET-CT scans had not demonstrated any obvious active disease, and a 3-month pause in therapy was decided as a reasonable approach.

However, a new scan after the pause in therapy revealed a relapse in disease with marked increased FDG uptake in a lesion in the pleura of the left lung (Fig. 2). Since cemiplimab was not reimbursed and available in Sweden at this time, the patient instead started treatment with the PD-1 inhibitor pembrolizumab 200 mg IV every third week. After 3 months of therapy, the pleural lesions were slightly larger and the patient had

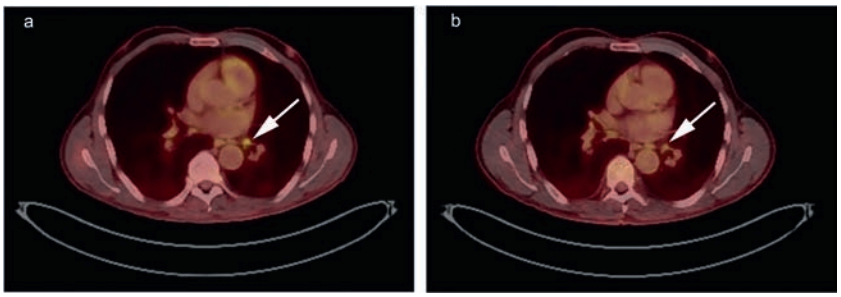

Figure 1 (a) FDG PET-CT scan with positive FDG uptake at baseline before initiation of cemiplimab. Note the FDG uptake in lymph nodes in the left lung hili (white arrow). (b) FDG PET-CT scan with reduced FDG uptake in the lymph nodes (white arrow) following 3 months of cemiplimab therapy.

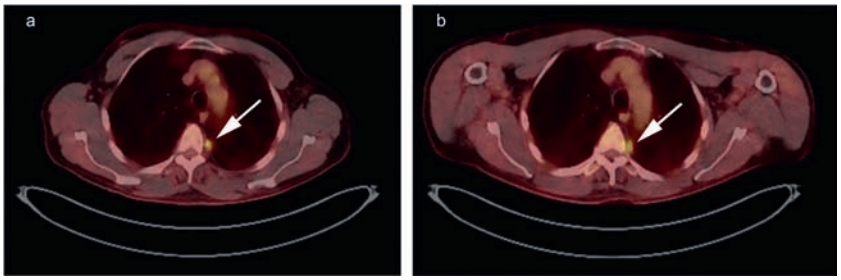

Figure 2 (a) FDG PET_CTscan demonstrating relapse of disease in the pleura of the left lung (white arrow) after 3 months of pause of therapy that followed a previous treatment period of cemiplimab for 1 year. (b) FDG PET-CT scan demonstrating further disease progression in the pleura of the left lung (white arrow) with increased size and FDG uptake following 3 months of pembrolizumab therapy, that is, PD-1 refractory disease.

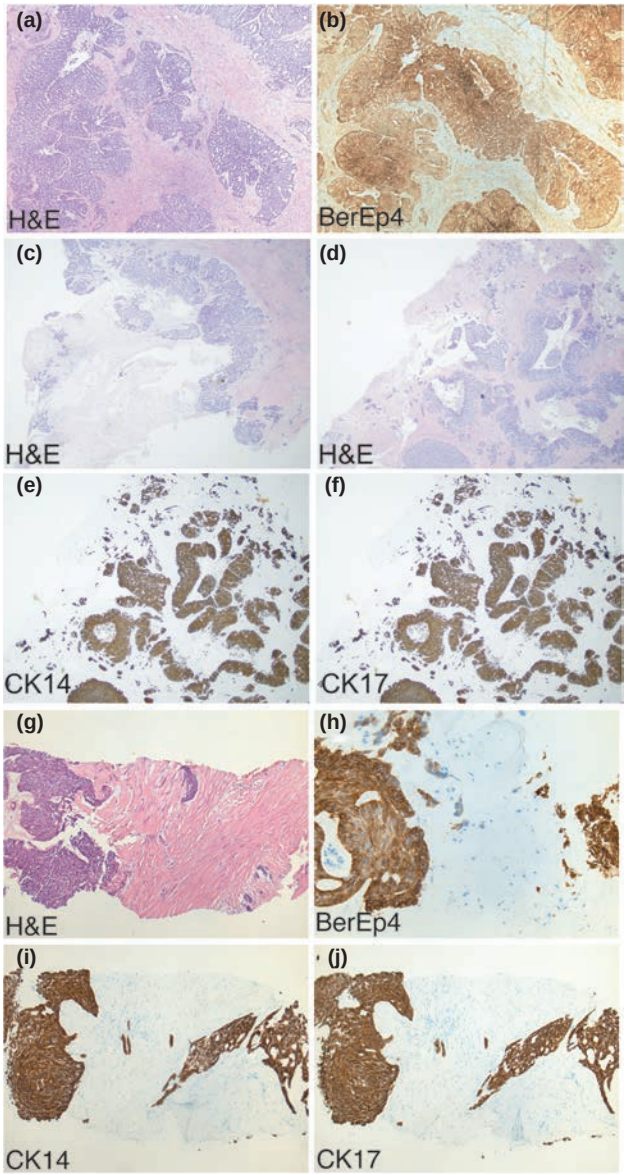

Figure 3 Histomorphological pictures of the infiltrating, high-risk basal cell carcinoma. H&E staining (a, c, d), immunohistochemical detection of BerEp4 (b), CK14 (e) and CK17 (f) of the primary tumour in the face. H&E staining (g) and immunohistochemical detection of BerEp4 (h), CK14 (i) and CK17 (j) of the metastatic pulmonary basal cell carcinoma. Original magnifications x 10 (a–d) and x 40 (e–j).

developed a severe diarrhoea of grade 3 that was judged to be an immune-related adverse event. The patient was prescribed prednisolone 1 mg/kg orally to that he responded well, and the pembrolizumab treatment was stopped. As the patient in the latest FDG PET-CT scan only had one tumour lesion with FDG uptake, he has been referred for thoracic surgery.

Following the uncertainties with the metastases judged to have complex characteristics, a pathological re-examination of the pleural biopsy has been performed using additional immunohistochemical staining against BerEp4, cytokeratin 14 (CK14) and cytokeratin 17 (CK17) as suggested by Linskey and co-workers.[1] The most commonly used staining, BerEp4 alone is unreliable for differentiation between BCC and bSCC, and the addition of CK14 or CK17 will increase the diagnostic certainty. BCC is usually positive for all three markers whilst bSCC would be negative with few exceptions. Both the primary tumour from the face and the lung metastasis demonstrated a strong positivity in BerEp4, CK14 and CK17, and negativity in S100, respectively, which together with the growth pattern of BCC in the patient´s face including the maxillary sinus, oriented the histological diagnosis towards BCC (Fig. 3).

Discussion

BCC constitutes one of the most common skin tumours, but metastatic BCC is extremely rare, ranging between 0.0028% and 0.55% of all patients with BCC.[2] Recent evidence has suggested that PD-1 inhibitors are effective treatments in not only melanoma but also in non-melanoma skin cancers in the advanced setting.[3,4] Here, we present a case with complex histology where the histopathological pattern indicated a potential overlap between BCC and bSCC, similar to what has been described previously.[1,5] The patient had received the hedgehog inhibitor vismodegib as first-line therapy, based on a diagnosis of previous metastatic BCC but was switched to the PD-1 inhibitor cemiplimab due to both concern for inadequate clinical efficacy, potentially related to what was suspected to be a bSCC tumour component and severe toxicity with impact on quality of life. In tumours with overlapping morphology of BCC and bSCC, immunhistochemical staining against BerEp4, CK14 and CK17 add value in the standard panel in order to optimize the management of patients with potential metastatic BCC or metastatic bSCC, where the use of systemic therapies may be different.

Following approximately one year of cemiplimab therapy, clinical disease control was obtained with radiological partial remission in parallel with improved quality of life and decreased toxicity. This clinical course is very similar to what recently has been reported in patients with locally advanced BCC post-hedgehog inhibitor therapy where cemiplimab therapy has been associated with an overall response rate of 31% and durable responses extending 12 months in a majority of patients in parallel with manageable toxicities.[6] With the termination of the Early Access programme for cemiplimab in SCC, the patient had a pause in therapy for approximately three months. However, a new scan at this time point revealed increased tumour size and FDG activity in one of the tumour lesions of the pleura eventually leading to restart of PD-1 inhibitor therapy. This time the PD-1 inhibitor pembrolizumab was chosen due to reimbursement issues, but the therapy was less successful with progress in

a pleural tumour lesion and immune-related toxicity that finally led to termination of the PD-1 inhibitor treatment. Whether the two different PD-1 inhibitors, cemiplimab and pembrolizumab have different effects in metastatic BCC is not known, it could also be that the resistance developed independently of the PD-1 therapy switch. In current conditions, metastatic surgery or radiotherapy may be an option that could be considered, although data are scarce on the clinical benefit of local therapy in PD-1 refractory disease.[7]

Acknowledgement

The patient in this manuscript has given written informed consent to the publication of the case details.

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CASE REPORT

Keratoacanthoma or cutaneous squamous cell carcinoma revealing a DNA mismatch repair default (Muir-Torre Syndrome)

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Abstract Keratoacanthoma (KA) and well-differentiated cutaneous squamous cell carcinoma (cSCC) are hardly distinguishable clinically and histologically. They both can be seen in patients with hereditary non-polyposis colorectal cancer (HNPCC) or Lynch Syndrome, corresponding to DNA microsatellite instability. In our case, a young man had the excision of two rapidly growing skin tumours for which distinction between KA and cSCC was initially clinically and pathologically challenging. The diagnosis of well-differentiated cSCCs was made and the patient was treated with surgery. Ten years after the first cSCC, he was diagnosed with Muir-Torre syndrome, a variant of Lynch syndrome, with an heterozygote mutation of the MSH2 gene. This later diagnosis allowed to screen his family members for the same mutation and to adopt an appropriate follow-up regarding the risk of digestive tumours for him and his family. Furthermore, it is important to know that, in case of non-resectable cSCC occurring in this patient, immunotherapy using anti-PD1 antibody would probably be effective due to the known increased immunogenicity of MMR deficient tumours.
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Conflicts of interest

Jérémy Lupu is consultant for Novartis; Emilie Routier is consultant for Novartis and BMS; Caroline Robert is consultant for BMS, Roche, Pierre Fabre, Novartis, Amgen, Sanofi, Merck, MSD, Astrazeneca. The other authors have not any conflict of interest.

Funding source

None.

What does this study add?

- Keratoacanthoma (KA) and cutaneous squamous cell carcinoma (cSCC) are often indistinguishable.
- Both KA and cSCC can be observed in the context of DNA microsatellite instability and can reveal this genetic background.
- Immunotherapy is expected to be effective in these tumours.

Case

Distinction between keratoacanthoma (KA) and well-differentiated cutaneous squamous cell carcinoma (cSCC) is challenging for the clinician as well as for the pathologist. KA is a rapidly growing skin tumour mostly described on sun-exposed sites of light-skinned elderly patients.[1] It usually presents as a skin nodule with a central crateriform area that corresponds pathologically to a keratin plug surrounded by a proliferation of well-differentiated keratinocytes forming lateral beaks. These clinical and pathological presentations are also compatible with those of a well differentiated and aggressive cSCC. However, spontaneous regression after a rapid growth can occur with KA but not with cSCC. Finally definitive differential between KA and cSCC sometimes relies only on this retrospective diagnostic feature: spontaneous regression.[1] Both KA and cSCC can be seen in patients with microsatellite instability in the context of Lynch syndrome.

Case: A 35-year-old man from Guyana with a type V Fitzpatrick phototype and no personal medical history had the excision of a large nodule that has been rapidly growing on his upper lip for the last 6 weeks (Fig. 1). Pathological analysis

initially suggested a KA. A few days only after the surgery, a nodule re-appeared and a second excision was performed and this time, pathology examination concluded to a well-differentiated invasive cSCC.

In <2 weeks, the patient saw a local relapse of the tumour and consulted in our centre. The facial magnetic resonance imaging, the whole-body CT and the PET CT did not find any suspicious secondary lesion. A large surgical resection was then performed with a plastic surgery reconstruction using a submental flap of Martin.

The initial pathology report concluded to a KA without obvious malignancy characteristics (Fig. 2) but signs of perineural tumour invasion (Fig. 3). However, after collegial discussion, the conclusion was changed for a well-differentiated cSCC. Then, the patient was followed by ultrasound imaging of cervical lymph nodes every 3 months: no suspicious lymphadenopathy was found.

Ten years later, the patient developed a 5 mm keratinizing nodule that appeared on his left cheek in 1 month. Initial biopsy found an aspect of well-differentiated cSCC but after complete excision, the final pathological result concluded to a KA. On the same time, a sebaceoma was found on a biopsy of a papule on his forehead.

During this second episode, the patient informed us that he had recently learned that five members of his maternal family presented with digestive cancers. We then suspected that he could be genetically deficient in DNA mismatch repair. Indeed, a genetic analysis detected a heterozygote mutation of the gene MSH2 that could be confirmed on a second sampling.

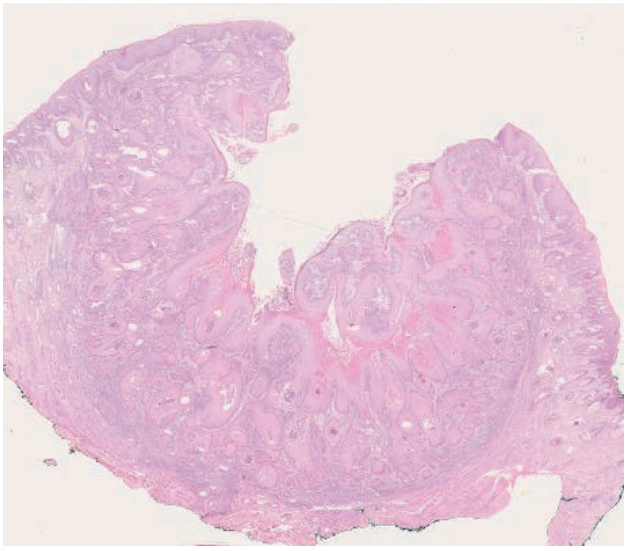

Figure 2 Histological picture of the keratoacanthoma/cutaneous squamous cell carcinoma of the patient's upper lip.

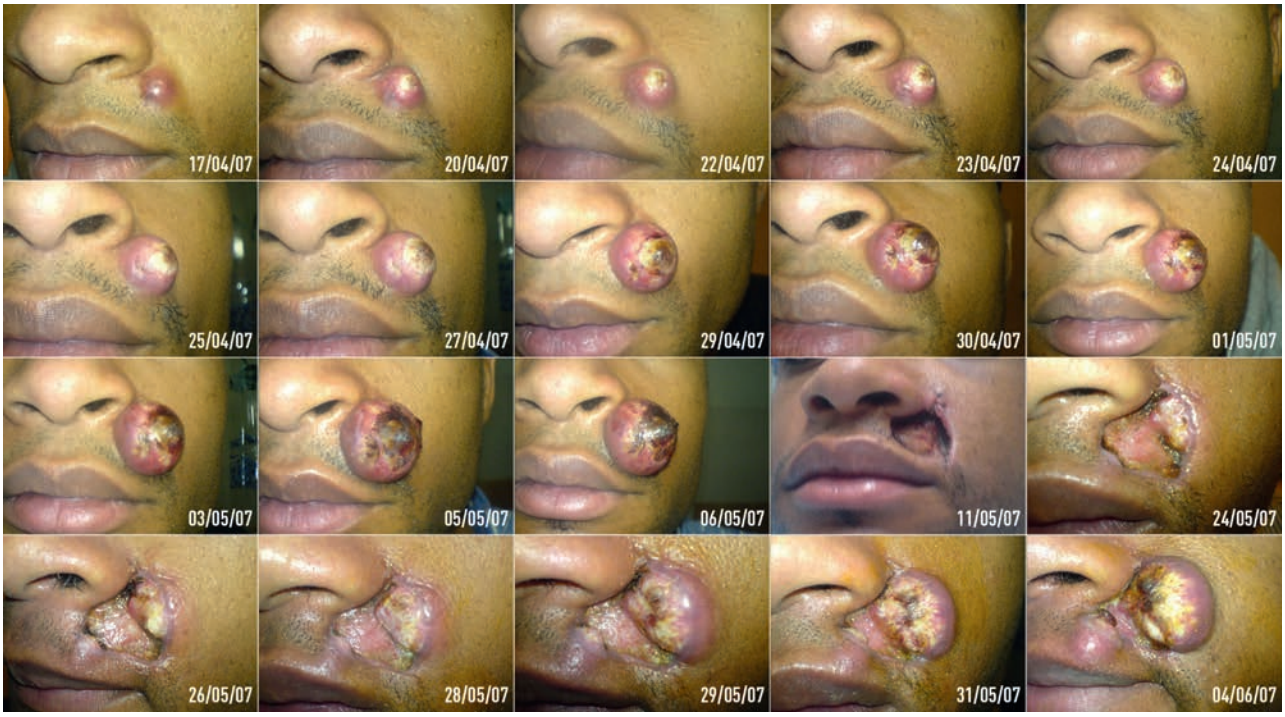

Figure 1 The cutaneous squamous cell carcinoma grew rapidly from April 17th (photo 1) to May 11th (photo 14), day of surgery. The nodule reappeared a week later and grew up from May 24th (photo 15) to June 4th (photo 20).

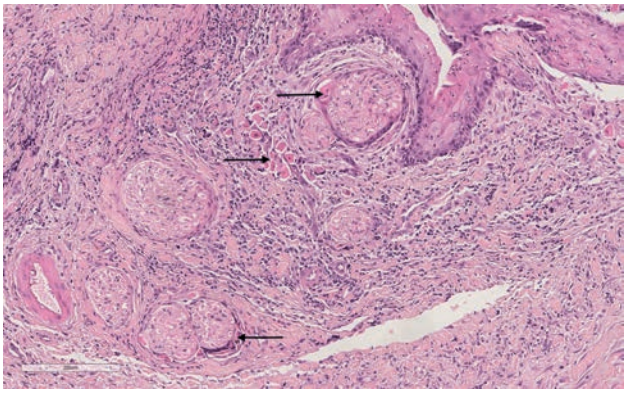

Figure 3 Keratinizing epithelial cells around nerves (cf arrows): signs of perineural tumour invasion.

A screening colonoscopy was performed, and a low-grade adenomatous and tubulovillous rectal polyp was found and resected.

Discussion

Generally, KA are benign keratinocyte skin tumours mostly seen in patients over 60.[2] In this young patient with two KA/cSCC, a sebaceoma, and a family history of digestive cancers, a genetic disease, such as a Muir-Torre syndrome (MTS), was suspected.[3–6] MTS is a variant of hereditary non-polyposis colorectal cancer or Lynch syndrome,[7] which is an autosomal dominant disorder due to DNA mismatch repair (MMR) default including deleterious germline mutation of MLSH1, MSH2, MSH6 or PMS2. After identifying the mutation responsible of MTS in our patient, this genetic defect could be screened among other family members. KA are well known in patients with MMR deficiency whereas only few cases of cSCC have been described in association with this genetic default.[8,9]

Several clinical studies have demonstrated the high efficiency of immunotherapy based on immune checkpoint blockade (ICB) treatment in patient with MMR deficient solid cancers.[10,11] Indeed, these tumours have a very high mutational load, high tumour lymphocyte density and increased neoepitopes and immune checkpoint expression as compared to DNA mismatch repair proficient tumours. Therefore, hypermutator phenotypes constitute optimal responders to ICB[12] PD-1/PD-L1$^{+/-}$ CTLA-4 blockade. Pembrolizumab and nivolumab are authorized for the treatment of metastatic MMR deficient solid tumours and cemiplimab, a more recent anti-PD1 monoclonal antibody has recently been authorized for the treatment of non-resectable or metastatic cSCC based on a high rate of durable responses.[13]

In conclusion, patients with cSCC and a personal or familial history of Lynch syndrome should be screened for MMR deficiency. In case of non-resectable or metastatic cSCC in these patients, immunotherapy based on PD-1 blockade, already approved for locally advanced or metastatic cSCC, has a particularly high probability of success and should be suggested.

Acknowledgement

The patient in this manuscript has given written informed consent to publication of his case details.

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