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Overview

Evolving Role of Systemic Therapies in Non-melanoma Skin Cancer

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Abstract

Keratinocyte cancers – basal and cutaneous squamous cell carcinoma (BCC, cSCC) – are the most common forms of non-melanoma skin cancer (NMSC) and there has been a significant increase in their incidence globally in recent decades. Although the majority of BCC and cSCC are cured with conventional surgery or radiotherapy, certain tumour or patient-determined factors may result in these modalities being inadequate or inappropriate, for example, locally advanced or metastatic disease, high tumour multiplicity, patient comorbidities and patient preferences. In these clinical circumstances, systemic treatment may be indicated, and over the past 10 years a number of new systemic agents have been approved. Nonetheless, effective systemic therapy for keratinocyte cancers remains an area of significant unmet clinical need. Improved understanding of the molecular and immune pathogenesis underlying tumour growth and development is critical for driving future advances and is a research priority. The aim of this review is to provide clinicians with an overview of systemic treatments for BCC and cSCC and will focus on current evidence for conventional chemotherapy, targeted therapies, immunotherapy, adjuvant and neoadjuvant therapy, chemoprevention and future prospects for novel systemic treatment approaches.

Key words: Basal cell carcinoma; dermatofibrosarcoma; Merkel cell carcinoma; NMSC; oncology; squamous cell carcinoma; systemic therapies

Statement of Search Strategies Used and Sources of Information

For this overview, all articles available in the literature were searched, using Pubmed as a source of research.

Introduction

Non-melanoma skin cancers (NMSC) are very common tumours, representing up to one-third of all human malignancies. Keratinocyte cancers, comprising basal and cutaneous squamous cell carcinomas (BCC, cSCC), are by far the most common form of NMSC, accounting BCC for 75–80% and SCC for 20–25%, respectively [1,2] and are the focus of this review. Rarer NMSC include Merkel cell carcinoma, cutaneous sarcomas, appendageal tumours, cutaneous lymphomas and angiosarcomas, and are discussed in separate reviews in this special issue of *Clinical Oncology*.

Recent data consistently demonstrate a steadily increasing incidence of keratinocyte cancers, due to factors including an ageing population, increasing ultraviolet radiation exposure, increasing numbers of immunosuppressed individuals and possibly increased awareness and earlier diagnosis [3]. Surgery is generally the therapeutic gold standard for most keratinocyte cancers and radiotherapy also plays an important role in routine clinical practice. However, certain tumour and patient-driven factors may result in some tumours being deemed unsuitable for surgery or radiotherapy after multidisciplinary discussion. For example, in patients with locally advanced and metastatic keratinocyte cancer – an increasing clinical problem [4] – there may be a significant risk of functional and cosmetic deficit from surgery and/or radiotherapy. In addition, conventional treatment may present challenges for some patients at high risk for multiple tumours and/or tumours with worse prognosis [e.g. immunosuppressed individuals such organ transplant recipients (OTR), patients with haematological malignancy such as chronic lymphocytic leukaemia, HIV, genodermatoses such as Gorlin syndrome and xeroderma pigmentosum]. Other patient-driven

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factors such as medical comorbidities, individual patient preferences and previous treatments may also influence the use of surgery and radiotherapy. In such circumstances, systemic therapy may be considered.

However, this patient group are often elderly or may have significant comorbidities and treatment toxicity from systemic therapy may be a significant limitation, particularly in some high-risk patient groups [5]. Indeed, these challenges are underscored by findings from a recent retrospective study of 190 patients with locally advanced cSCC (la-cSCC, $n = 76$) and metastatic cSCC (m-cSCC, $n = 114$) treated in Germany and Austria in 2010–2011: 59% with la-cSCC did not receive any active intervention and fewer than 20% received systemic anti-tumour therapy [6]. Although there is recent encouraging evidence that this therapeutic landscape may be changing – particularly with advances in immunotherapy – treatment of advanced keratinocyte cancer remains an area of significant unmet clinical need.

The aim of this overview is to provide clinicians with an update on the systemic treatment currently available for keratinocyte cancer. We focus on evidence for treatment with conventional chemotherapy, targeted therapies and checkpoint inhibitor immunotherapy in advanced keratinocyte cancer. We also address recent developments in adjuvant, neoadjuvant and chemoprevention and discuss future prospects for progress in this field.

Chemotherapy

Conventional Chemotherapy

There is no systemic chemotherapy agent currently approved for advanced cSCC. Mono- or polychemotherapy regimens have included platinum-based drugs (e.g. cisplatin, carboplatin), antimetabolite pyrimidine analogues [e.g. 5-fluorouracil (5-FU), capecitabine], taxanes (e.g. paclitaxel), bleomycin, methotrexate, adriamycin, doxorubicin, gemcitabine and ifosfamide [6–12]. However, most of the reported clinical trials have significant limitations, including retrospective design, non-randomisation, small size, heterogeneous patient populations and variable outcome assessments [7–12]. In general, observational studies show up to 80% remission for combination treatments and up to 60% remission for monotherapy. However, sustained remissions are rare and most reported responses are short-lived with rapid recurrences [11–13]. In addition, most chemotherapeutic agents are associated with considerable toxicity, which may be a significant limitation for a patient population that is often elderly and/or with significant medical comorbidities requiring, for example, dose adjustments and consideration of drug interactions [5].

Platinum-based therapy is one of the more commonly used approaches. A recent systematic review/meta-analysis of 60 cases treated with cisplatin alone showed an overall response rate (ORR) of 45% (22% complete response and 23% partial response), with a median disease-free survival after complete response of 14.6 months [11]. In a single-centre retrospective study of 25 patients, platinum-based therapy provided improved progression-free survival (PFS) and overall survival compared with taxanes and cetuximab [12]. Polychemotherapy is generally associated with higher response rates. For example, cisplatin/5-FU and cisplatin/doxorubicin had reported response rates of 85.7 and 58%, respectively, but were less well tolerated than monochemotherapy [8]. In an attempt to minimise adverse effects in elderly patients, oral administration of 5-FU has also been used. Cartei *et al.* [13] reported 14 patients treated with oral 5-FU for 12–36 weeks: responses were seen in 64%, but these were partial responses only in 14.2% and the remainder were minimal partial response/stable disease. Systemic chemotherapy for la-BCC and m-BCC has been reported only in case series and most patients are treated as for m-SCC with platinum-based regimens. Response rates are usually no higher than 20–30% and response durations typically 2–3 months [14,15].

Intralesional Chemotherapy and Electrochemotherapy

Intralesional administration of chemotherapy is also reported for keratinocyte cancer. For example, intralesional 5-FU, interferon, interleukin-2 and bleomycin have all been effectively used in BCC [16]. Intralesional methotrexate has also been reported for primary cSCC, particularly well-differentiated and keratoacanthomas types, with a response rate of up to 92% in one series [17]. Electrochemotherapy (ECT) is a technique in which high-intensity electrical pulses are sent into the tumour via electrodes to increase drug absorption. Bleomycin or cisplatin has usually been administered by ECT for primary, locally advanced and metastatic BCC and SCC [18–20]. For example, a European multi-institutional prospective non-randomised trial (EUREKA) included patients who had failed or were unsuitable for surgery or radiotherapy and reported complete and partial response rates for cSCC of 55 and 24%, respectively, and 91 and 3%, respectively, for BCC [18–20]. The use of ECT in NMSC is further discussed in a separate review in this special issue [21].

Targeted Therapies

Two targeted treatments are approved for advanced BCC – the hedgehog pathway inhibitors vismodegib and sonidegib. However, there are currently no targeted therapies licensed for advanced cSCC.

Hedgehog Pathway Inhibitors

The hedgehog pathway is involved in cell differentiation and proliferation and dysregulation of this pathway may contribute to tumours such as BCC, pancreatic cancer and medulloblastoma [1]. The PTCH1 gene, a sonic hedgehog pathway family member, encodes the PTCH1 cell surface transmembrane protein, which inhibits the transmembrane protein, SMO (smoothened). SMO is an activator of the sonic

hedgehog pathway. In the absence of hedgehog signalling, PTCH1 protein keeps the activity of SMO suppressed; when the hedgehog ligand is present and bound to PTCH-1, SMO is no longer inhibited and allows transcription factor *Gli* to enters the nucleus, stimulating cell proliferation and tumorigenesis [1]. Most sporadic BCCs have dysregulation of the hedgehog signalling pathway, usually through mutations in either PTCH1 or, less frequently, SMO [1]. Germline mutations in the pathway are associated with the rare genodermatosis, naevoid BCC syndrome (Gorlin syndrome), characterised by the early onset of multiple BCC [1]. Two small molecule SMO inhibitors have been developed to target this pathway – vismodegib and sonidegib – and are currently licensed for treatment of la-BCC and/or m-BCC.

Vismodegib

Vismodegib was the first oral SMO inhibitor to be approved in 2012 for the treatment of la-BCC and m-BCC by the US Food and Drug Administration (FDA) and the European Medicines Authority (EMA). The pivotal phase II clinical trial (ERIVANCE) was a multicentre, single-arm trial, which enrolled patients ($n = 104$) with m-BCC or la-BCC not suitable for either surgery or radiotherapy [22,23]. Patients were treated with 150 mg/day vismodegib. At 12 months, the ORR was 47.6% for la-BCC and 30% for m-BCC, with a median duration of response of 9.5 and 7.6 months, respectively. These results were updated at 39 months of follow-up, with response rates of 60.3% for la-BCC and 48.5% for m-BCC and median response durations of 26.2 and 14.8 months, respectively [24]. The results of the pivotal ERIVANCE trial have been confirmed in a global safety study (STEVIE), with response rates of 68.5% for la-BCC and 36.9% for m-BCC [25]. Significant improvements in health-related quality of life in 1215 patients with advanced BCC treated with vismodegib were also reported in STEVIE [26]. Vismodegib has also been studied in a randomised controlled trial that enrolled 41 patients with Gorlin syndrome, showing significant activity in reducing the size of existing BCC and in preventing new BCC [27,28].

Although currently licensed by the FDA and EMA, it is noteworthy that approval for vismodegib was withdrawn in 2018 after re-evaluation by the National Institute for Health and Care Excellence (NICE) in the UK because of uncertainty relating to overall survival in clinical trials, lack of comparison with best supportive care and health economic analyses of cost-effectiveness [29].

Sonidegib

Sonidegib is a second oral SMO inhibitor and was approved by the FDA and EMA in 2015 for the treatment of la-BCC, but not m-BCC. The pivotal clinical trial (BOLT) was a prospective, multicentre study that enrolled 194 patients with la-BCC or m-BCC randomised to treatment with 200 or 800 mg daily and initial response rates of 36% [30]. Patients receiving 200 mg/day had fewer side-effects and treatment was better tolerated; the 200 mg dose was approved based on the risk/benefit ratio. After a median follow-up of 30 months, the response rate for la-BCC was 56.1% (central review) and for m-BCC was 7.7%, with a median duration of responses of 26.1 and 24.0 months, respectively, and 2-year survival rates of 93.2 and 69.3%, respectively [31].

Hedgehog Pathway Inhibitor Adverse Effects and Resistance

Hedgehog inhibitor class-specific adverse effects were observed in clinical trials of both drugs and included taste disturbance, weight loss, muscle spasms, alopecia and fatigue. These led to discontinuation of treatment in about 30–50% of patients [22,27], resulting in the recurrence of BCC in some cases [28]. Strategies to manage adverse effects have been proposed [32] and intermittent use of hedgehog inhibitors may potentially limit them. This has been tested in the MIKIE trial and equal efficacy was demonstrated for a schedule with a 3-month induction phase followed by a drug holiday compared with continuous treatment [33]. Patients exposed to vismodegib may also be at increased risk of developing cSCC [34], although this finding has not proved to be consistent [35]. Resistance to hedgehog pathway inhibitors is also increasingly recognised, although uncommon [36].

Epidermal Growth Factor Receptor Inhibitors

Most evidence to date relating to targeted therapies for cSCC has focused on epidermal growth factor receptor (EGFR) inhibition [37]. The EGFR/RAS/MAPK signalling pathway plays an important role in the proliferation and survival of tumour cells. There are two classes of EGFR inhibitor: monoclonal antibodies that block the extracellular receptor domain and competitively inhibit EGFR and intracellular RAS/MPAK signalling (e.g. cetuximab, panitumumab) and small molecule tyrosine kinase inhibitors (TKIs) that block activity of the tyrosine kinase ATP binding site and inactivate intracellular signalling (e.g. erlotinib, gefitinib, lapatinib, dacomitinib) [37].

Epidermal Growth Factor Receptor Monoclonal Antibody Inhibitors

EGFR inhibitors are licensed for use in head and neck SCC, colorectal and lung cancer. Extrapolating from experience with these other squamous malignancies, and given the finding of overexpression of EGFR in m-cSCC [38], EGFR inhibitors have also been used off-label in advanced cSCC. Whereas in head and neck SCC, EGFR truncated variant III leads to constitutive activation and resistance to EGFR inhibition, EGFR mutations are uncommon and this variant has not been found and predictive biomarkers not established for cSCC [37,39].

Most studies are with cetuximab, a human–mouse chimeric monoclonal IgG1 antibody. It has been used alone [40–43] and in combination with both radiotherapy and platinum-based chemotherapy [44–49]. A phase II open-label prospective trial of cetuximab monotherapy as first-line treatment for unresectable cSCC ($n = 36$) showed 69% disease control at 6 weeks, with an overall objective response rate of 28%. However, responses were short-lived, with a median PFS of 4.1 months [41]. A median PFS of 9 months was reported in a retrospective series of 31 patients with advanced cSCC, in whom a response rate of 48.5% was

seen with cetuximab monotherapy [40]. Disease control rates of 33% at weeks 20–36 and disease-free survival of 6 months were reported retrospectively in six patients with m-cSCC treated with cetuximab alone or combined with radiotherapy [43]. Indeed, combination with cisplatin or radiotherapy seems to provide higher response rates compared with cetuximab alone. However, in a prospective study of 20 patients with unresectable cSCC treated with cetuximab alone or with radiotherapy or carboplatin, the duration of response was short (overall survival 11.1 months, PFS 5.7 months) [48], although in a series of eight patients with la-cSCC treated with cetuximab and radiotherapy, more durable disease control was reported, with complete response in five of eight patients maintained at a median of 25 months of follow-up [45]. Panitumumab is a fully humanised monoclonal EGFR antibody approved in colorectal cancer and has also been evaluated in cSCC: an open-label phase II trial in 16 patients with advanced cSCC reported ORRs of 31%, with a median PFS of 8 months [50].

Most adverse events with EGFR antibodies are cutaneous and dose-dependent: papulopustular rashes occur early and affect cosmetically sensitive areas, such as the head and neck, and xerosis and pruritus are common. Data on the use of anti-EGFR inhibitors in certain high-risk patient groups, such as OTRs, are limited. Although generally well-tolerated [11], fatal diffuse alveolar damage occurred in two lung transplant recipients on cetuximab [51]. Nonetheless, cetuximab seems to be better tolerated in elderly patients compared with most chemotherapeutic agents [41].

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Gefitinib and erlotinib are selective EGFR TKIs. Both have activity in non-randomised phase II studies in advanced cSCC, with ORRs of 16 and 10%, respectively [52,53]. However, once again, these responses were short-lived, with a median PFS of 4.7 and 3.8 months, respectively. Dacomitinib has also been evaluated in 42 patients with recurrent or m-cSCC: ORR was 28% (2% complete response; 26% partial response); median PFS and overall survival were 6 and 11 months, respectively [54]. Toxicity of these agents is also predominantly acneiform rashes, diarrhoea and fatigue.

Overall, EGFR inhibitors seem to have a modest effect as monotherapy or in combination (ORR 7–28%; median PFS 3.8–4.7 months). However, as with data for chemotherapy, most trials are limited by relatively small numbers, heterogeneous patient populations and outcome measures, retrospective design and non-randomisation.

Immune Checkpoint Inhibitor Immunotherapy

In 2018, the anti-programmed cell death receptor-1 (anti-PD-1) immune checkpoint inhibitor (ICI), cemiplimab, become the first systemic therapy to be formally approved for advanced cSCC by the FDA and was approved by the EMA in July 2019.

Immune checkpoints including the PD-1/PD-L1 and CTLA-4 pathways are critical in the immune control of cancer [55]. Therapeutic targeting of these key immune checkpoint proteins has led to significant improvements in many cancers, notably melanoma, both for the treatment of metastatic disease, and also in the adjuvant and potentially neoadjuvant settings. Tumour mutational burden is an important biomarker for the response to ICI-based immunotherapy, as the resulting neoantigen formation is recognised by the immune system [56]. Melanoma has a high tumour mutational burden driven by ultraviolet exposure, but cSCC and BCC have even higher rates of somatic mutations [57]. They should, therefore, be responsive to ICI and emerging data now indicate that this is probably the case [58].

Anti-PD-1 Immunotherapy in Cutaneous Squamous Cell Carcinoma

The therapeutic potential of ICI in keratinocyte cancer was initially supported by case reports and small case series in which anti-PD-1 therapy in patients with advanced or metastatic disease had significant activity [59–64].

Cemiplimab is a human monoclonal anti-PD-1 antibody. A phase I/II study included a phase I extension cohort with la-cSCC or m-cSCC ($n = 26$) and phase II cohort with m-cSCC ($n = 59$). More than 50% in both groups had received previous chemotherapy and more than 60% previous radiotherapy. Patients were treated with intravenous cemiplimab 3 mg/kg every 2 weeks [65]. ORR was 50% in the phase I cohorts and 48% in the phase II cohorts, with 7% in the latter achieving a complete response. The median time to response was 1.9 months and durable response lasting at least 105 days was seen in 65% and 615 in the phase I and II cohorts, respectively. Cemiplimab was generally well tolerated: only 7% stopped treatment and observed adverse effects were similar to other anti-PD-1 drugs and included diarrhoea (27%), fatigue (24%), nausea (17%) and rash (15%). Based on these data, cemiplimab was approved in September 2018 by the FDA and by the EMA in July 2019 for m-cSCC and la-cSCC in patients who are not candidates for curative surgery or radiotherapy. A phase II study testing fixed dose and alternative dosing intervals of cemiplimab is in progress (NCT02760498). On 7 August 2019, NICE recommended cemiplimab as an option for treating la-cSCC or m-cSCC in adults when curative surgery or curative radiotherapy is not appropriate [66].

Pembrolizumab was a first-in-class PD-1 inhibitor approved in 2011 by the FDA for advanced melanoma alone or with ipilimumab, a CTLA-4 inhibitor. It has subsequently been approved for malignancies including metastatic non-small cell lung cancer and head and neck SCC. Its use in SCC has been described in case reports [59–64] and a phase II study is currently testing its use in recurrent/metastatic or locally advanced unresectable cSCC (NCT03284424). Nivolumab is a human monoclonal antibody, approved for metastatic melanoma and also head and neck SCC: it has

been used off-label in case reports of advanced cSCC with evidence of activity [67].

CTLA-4 Immunotherapy in Cutaneous Squamous Cell Carcinoma

Ipilimumab was the first-in-class monoclonal human antibody CTLA-4 inhibitor, approved by the FDA for metastatic melanoma in 2011. A few case reports suggest activity in cSCC. For example, a patient with metastatic melanoma and m-cSCC had a complete response to both diseases at 8 months after four cycles of ipilimumab [68].

Immune Checkpoint Inhibitor Immunotherapy in Basal Cell Carcinoma

As BCC have an even higher tumour mutational burden than cSCC, they are potentially good candidates for ICI immunotherapy. Although clinical trials data are lacking, there are case reports of activity with anti-PD-1 agents [69–72] and also anti-CTLA-4 therapy [73].

Adverse Effects of Immune Checkpoint Inhibitor Immunotherapy

The most frequent adverse events when ICI are used for cSCC, particularly immune-related adverse events, seem to be similar to those seen in melanoma. Immunosuppressed patients were excluded from pivotal clinical trials and may require specific consideration [74]. For example, the risk of graft rejection in OTRs and immune-related adverse events relevant to graft function (e.g. nephritis), together with reduced anti-tumour activity related to, for example, immunosuppressive drugs, haematological malignancy or HIV all need to be considered [11,74]. To date, evidence in this patient group is restricted to case reports and case series, much of it extrapolated from experience in melanoma, and suggests that graft rejection may be higher with anti-PD-1/PD-L1 immunotherapy, but that the response seems to be comparable with immunocompetent individuals [62,74–76].

Combined Radiotherapy and Systemic Therapy

Several systemic therapies – particularly cisplatin/carboplatin and cetuximab – have been combined with radiotherapy for the treatment of advanced keratinocyte cancer with curative intent. This approach is largely extrapolated from experience in head and neck SCC, as data for cSCC are relatively limited [43,44,46,77–80].

In the first prospective phase II study of concurrent chemoradiotherapy, patients with la-cSCC unsuitable for surgery were treated with definitive radiotherapy (70 Gy in 35 fractions) and concurrent weekly cisplatin. An overall complete response rate of 63% was reported in 19 evaluable patients [77]. However, a recent randomised phase III trial (TROG 05.01) in la-cSCC comparing postoperative concurrent chemoradiotherapy with radiotherapy alone did not show benefit from the addition of weekly carboplatin [78]. As already discussed, combined treatment with cetuximab has been described for cSCC [43,44,46,48]. There are also case reports of radiotherapy used in combination with vismodegib in recurrent or la-BCC [79]. In melanoma, ICI have also been used in combination with radiotherapy, but significant data are not yet available for advanced keratinocyte cancer.

Adjuvant and Neoadjuvant Systemic Therapy

There are currently no licensed adjuvant systemic therapies for BCC or cSCC. In cSCC, high-risk clinical and pathological factors include size, depth of invasion, location, perineural invasion, differentiation, surgical margin involvement, recurrent disease and immunosuppression [1]. A phase III randomised trial of adjuvant 13-cis-retinoic acid and interferon-alpha (following surgery and/or radiotherapy) showed no benefit [80], nor was there benefit from adjuvant chemotherapy or cetuximab combined with radiotherapy in a small retrospective study [81]. However, benefit was reported in resected high-risk cSCC with radiotherapy combined with cetuximab (versus radiotherapy alone) in a separate retrospective study, with PFS at 5 years of 66% versus 29% [82]. There are no published data but several ongoing clinical trials of adjuvant anti-PD-1 agents high-risk and locally advanced scc (la-cSCC) for cemiplimab after surgery and radiotherapy (NCT03969004) and pembrolizumab (NCT03057613, NCT03833167).

There are limited data for neoadjuvant activity of systemic therapy in keratinocyte cancer [18,83–86]. As highlighted previously, intralesional methotrexate had neoadjuvant activity in one retrospective study [18]. In addition, neoadjuvant cetuximab alone or combined with cisplatin or carboplatin and 5-FU in 34 patients with unresectable cSCC resulted in tumours becoming resectable in 92% of the cetuximab/chemotherapy group and 55% with cetuximab monotherapy [83]. The EGFR inhibitor, lapatinib, reduced cSCC size in two of eight patients treated with neoadjuvant intent in an open-label prospective study [84]. For BCC, neoadjuvant use of vismodegib in 15 patients treated reported recurrence in only one patient [85], but there are currently no randomised data to support this. No data are yet available for neoadjuvant ICI therapy in keratinocyte cancer.

Keratinocyte Cancer Chemoprevention with Systemic Agents

Systemic chemoprevention is usually considered in patients at high risk for new keratinocyte cancer, including a history of keratinocyte cancer or risk of developing multiple, potentially aggressive keratinocyte cancers, as in OTR

and other immunosuppressed patients. Current practice includes use of systemic retinoids [87–89], capecitabine [90,91], nicotinamide [92–94] and, where relevant, revision of immunosuppressive medication [86,95–101]. This is discussed in detail in the review by Collins *et al.* [102] in this special issue. As indicated previously, oral vismodegib has an established chemopreventative effect in Gorlin syndrome [27,28].

Future Prospects for Systemic Treatment in Keratinocyte Cancer

Systemic Treatment in Cutaneous Squamous Cell Carcinoma

Limited understanding of the molecular pathogenesis of cSCC has hindered the development of treatments for advanced cSCC [37]. In particular, the high tumour mutational burden has made identification of relevant driver mutations and, consequently, targeted therapies, more challenging. Recent improved understanding of cSCC genomics [57], may lead to future progress in this area. Significant advances are particularly being made with immunotherapy in advanced cSCC. For example, trials with established agents include pembolizumab both alone (NCT02964559, NCT03284424), in combination with histone deacetylase inhibitor abexinostat (NCT03590054) and cetuximab (NCT03082534); nivolumab alone (NCT03834233); anti-PD-L1, avelumab, with or without cetuximab (NCT0394491); anti-PD-L1 atezolizumab with the MEK inhibitor, cobimetanib (NCT03108131); neoadjuvant cemiplimab for recurrent head and neck SCC (NCT03565783), or as neoadjuvant intralesional therapy for recurrent cSCC (NCT03889912); avelumab with radical radiotherapy (NCT03737721). New immunotherapeutics in trials include cosibelimab (NCT03212404) and SL-279252, a PD-1-FC-OX40L checkpoint fusion protein (NCT03894618). TVEC is being evaluated in locally advanced keratinocyte cancer (NCT03458117). Trials of targeted treatments include lenvatinib (a vascular endothelial growth factor receptor TKI) and cetuximab (NCT03524326).

Systemic Treatment in Basal Cell Carcinoma

Trials for la-BCC and m-BCC include nivolumab alone or with ipilimumab (NCT03521830); pembrolizumab with or without vismodegib (NCT02690948); cemiplimab (NCT03132636); neoadjuvant vismodegib (NCT03035188); radiotherapy concurrently or after vismodegib (NCT0 1835626); neoadjuvant sonidegib followed by surgery or imiquimod (NCT03534947); itraconazole and arsenic trioxide, which both inhibit hedgehog pathway signalling, are also being investigated (NCT02354261, NCT02699723).

Conclusions

Most keratinocyte cancers are cured by conventional surgery or radiotherapy. However, systemic agents are playing an increasingly important role in the management of keratinocyte cancer, both in the context of advanced disease and chemoprevention, but also potentially in adjuvant and neoadjuvant settings. The anti-PD-1 inhibitor, cemiplimab, is the only approved drug for advanced cSCC and the small molecule hedgehog inhibitors, vismodegib and sonidegib, are approved for advanced BCC. Patients unresponsive or with contraindications may be considered for systemic chemotherapy or, in the case of cSCC, for EGFR inhibitors. However, both approaches are limited by response rates and durability. Chemotherapy in particular may be challenging in elderly patients and those with comorbidities. Studies of multimodality treatment, particularly in combination with radiotherapy, are few. Systemic chemoprevention will probably become an increasingly important consideration as the incidence of keratinocyte cancer continues to rise steadily. As outlined in this review, there remain many important unanswered questions regarding the role of systemic therapies in the management of keratinocyte cancer, including the possible health economic implications. Nonetheless, recent advances in basic research and increased clinical trials activity in this area hold promise for significant progress in the near future.

Conflict of Interest

The authors declare no conflicts of interest.

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