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Overview

Management of Non-melanoma Skin Cancer in Transplant Recipients

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Abstract

Transplant recipients have a significantly higher risk of developing non-melanoma skin cancers compared with the general population and squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are the most common post-transplant malignancies. Although in the general population BCC outnumbers SCC 4:1, in transplant patients this ratio is reversed and SCC is more common, with a 65- to 250-fold increased incidence. As patients in immunosuppressed states are living longer after transplants, the incidence of skin cancer in this population continues to increase. The skin cancers in transplant patients also tend to be more aggressive, with higher morbidity and mortality. Preventive strategies play an important role in transplant recipients given their increased frequency of developing both premalignant and malignant skin lesions. Sun protection and regular skin cancer screening are critical. In addition, chemoprophylaxis with systemic retinoids, nicotinamide and capecitabine can significantly reduce the development of new skin cancers. Topical 5-fluorouracil, imiquimod, photodynamic therapy and cyclooxygenase inhibitors have all been investigated in transplant patients for the treatment of field cancerisation. Adjusting the immunosuppressive regimen is also an important adjuvant therapeutic strategy for managing skin cancers in transplant recipients and requires integrated multidisciplinary care with the entire transplant team. This article reviews the epidemiology of non-melanoma skin cancer in transplant patients, discusses the prevention strategies and highlights the management and treatment strategies of both field cancerisation and non-melanoma skin cancers.

Key words: Dermatology; immunosuppression; non-melanoma skin cancer; squamous cell carcinoma; transplant recipients

Statement of Searches Used and Sources of Information

A search of PUBMED, EMBASE and MEDLINE was carried out using the key words: dermatology; immunosuppression; non-melanoma skin cancer; squamous cell carcinoma; basal cell carcinoma; transplant recipients and various combinations of the aforementioned key words to review relevant studies.

Introduction

Organ transplant recipients (OTRs) face a higher risk of malignancy compared with the general population, secondary to long-term immunosuppression leading to reduced immune-mediated tumour surveillance [1]. In OTRs of European decent, non-melanoma skin cancers (NMSC), including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are the most common post-transplant malignancies, accounting for 40–50% [2,3]. Other skin cancers commonly reported include Kaposi sarcoma, Merkel cell carcinoma (MCC) and malignant melanoma [4]. For the purpose of this review, we have focused on the epidemiology, prevention and management of NMSC.

With an aging population, NMSC incidence is increasing and is projected to cost the National Health Service £180 million by 2020 [5]. NMSC in OTRs tend to be more aggressive, with higher morbidity and mortality. This has led to the implementation of post-transplant skin cancer surveillance, which has been further refined according to risk predictors [6]. However, the prevention and treatment of NMSC remains challenging.

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Epidemiology of Non-melanoma Skin Cancer in Transplant Patients

Transplant patients have a higher mortality due to skin cancer than mortality related to either breast or colon cancer [7]. Although in the general population BCC outnumbers SCC 4:1, in transplant patients this ratio is reversed and SCC is more common, with a 65- to 250-fold increased incidence. In comparison, BCC has a 10- to 16-fold increase in OTRs [8]. SCC carries substantial morbidity and mortality, with reported metastatic rates of up to 8% compared with 1% in the general population and a 3-year mortality rate of 46% for metastatic disease [1]. The local recurrence rate is estimated to be 14.1% within the first 19 months [9].

In NMSC, demographics and Fitzpatrick skin type play a role in risk stratification, with the highest risk being fair skinned, male and elderly patients. Male recipients have a three-fold increased risk [10]. Ultraviolet radiation is the most important risk factor for NMSC. Ultraviolet radiation leads to local and systemic immunosuppression, which in combination with their immunocompromised state further promotes carcinogenesis. SCC is associated with a cumulative lifetime sun exposure compared with BCC, which is linked to intermittent and childhood sun exposure [11].

The duration of immunosuppression contributes to the increased risk of NMSC, due to immune-mediated mechanisms of carcinogenesis. Pre-transplantation SCC is the strongest predictor of post-transplantation SCC risk [12]. In renal transplant patients, SCCs are around four times more likely to develop in those who have confluent areas of actinic damage than in those without field change. Renal transplant patients with viral warts have been reported to have a significantly higher incidence of concurrent actinic keratoses [13]. β-human papillomavirus (HPV) has been shown to be associated with NMSC development; HPV DNA has been found in 80% of NMSC in immunosuppressed individuals and in 50% in immunocompetent individuals. Although the association between viral warts and SCC has been well recognised, oncogenic HPV subtypes have also been identified in 60% of BCCs in the immunocompromised [14].

The risk of developing SCC in transplant patients increases steadily with time after transplantation. The incidence in the USA and Western Europe increases from 10–27% at 10 years to 40–60% at 20 years after transplantation [15]. Heart transplant recipients have the highest risk of developing post-transplant NMSC, followed by lung transplant recipients, which is secondary to the more intensive immunosuppression regimens as well as the typically older age at the time of transplant. Kidney and liver transplant recipients have a lower risk, with most cohorts indicating that kidney transplant recipients have a higher risk than those receiving a liver [16].

Kaposi sarcoma arises from lymphatic endothelial cells and has an increased incidence of 84- to 500-fold. It is associated with human-herpes-virus 8 (HHV-8) infection. There is an increased risk of 23–28% in HHV-8 seropositive patients prior to transplantation versus 0.7% in seronegative patients [17].

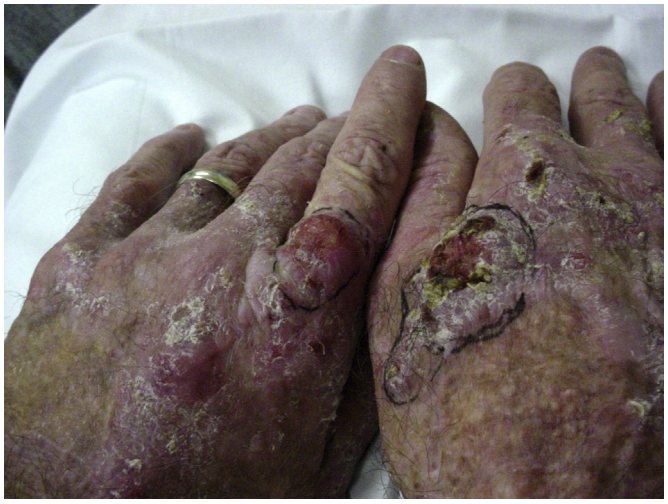

Fig 1. Extensive squamous cell carcinoma (marked with black ink) with surrounding field cancerisation on the dorsal hands of a renal transplant recipient.

MCC in OTRs is increased by 24-fold. It is a neuroendocrine skin tumour linked to Merkel cell polyomavirus infection. Risk factors include male gender, being Caucasian, duration of transplantation >10 years and over 50 years of age at the time of transplantation [18].

Although organ transplant patients are the most studied population with regards to immunosuppression and the development of cutaneous malignancies, immunosuppression can also result from a variety of other conditions. Patients with chronic lymphocytic leukaemia have an eight-fold increased risk of NMSC compared with the general population [19,20]. The HIV-infected population has a risk of developing BCC and SCC that is increased two- and five-fold, respectively [21,22]. In addition, patients with iatrogenic immunosuppression for autoimmune and autoinflammatory diseases are at increased risk of developing NMSC. Tumour necrosis factor inhibitors, which are frequently used to treat these conditions, are associated with an increased risk of SCC [23,24].

Prevention Strategies for Non-melanoma Skin Cancer in Organ Transplant Recipients

The Role of Sun Protection

The effect of ultraviolet radiation on NMSC pathogenesis is evident by the predominantly sun-exposed distribution. Studies have shown the impact of sunscreen use in immune-competent patients with a reduction in actinic keratoses and SCC. Unfortunately, several studies have shown the poor compliance with sun protection in OTRs for reasons including lack of sun protection education, financial limitations and practical considerations [25,26].

Ulrich *et al.* [27] showed the impact of giving free sunscreen and application demonstrations to OTRs through

their prospective case–control study. The control group developed new actinic keratoses and eight new invasive SCCs compared with the sunscreen group, who remained free of new SCCs. It is vital to promote the intensified use of sunscreens in combination with educational programmes and behavioural changes [27]. There is also a risk of vitamin D insufficiency due to their sun-protective behaviour; therefore, supplementation should be considered. Emerging evidence shows the relevance of vitamin D in photocarcinogenesis and NMSC development. This gives rise to potential modulation by vitamin D and its analogues to provide future preventative strategies [28].

The Role of Skin Surveillance and Skin Cancer Screening

In the UK, the National Institute for Health and Care Excellence recommends skin surveillance for OTRs in dedicated dermatology clinics [29]. There is consensus among American and European transplantation organisations recommending skin cancer screening every 6–12 months. In patients with previous SCC, a full skin examination is recommended every 3–6 months for up to 5 years, as 95% of local recurrences/metastases are thought to occur within this period. However, this current approach does not consider individual patient risk. The OTR population is increasing, with a longer life expectancy; the challenge for healthcare resource allocation is substantial. Harwood *et al.* [6] proposed an evidence-based risk stratification approach including skin type, age at transplant and sunburn history. They propose annual surveillance in only the highest risk group. Following a first NMSC, surveillance every 4 months was found to be sufficient. It can then be reduced to annually if cancer-free for a year. This approach provides capacity for the high-risk patients, with a rapid access system if needed [6].

Chemoprevention

Chemoprophylaxis in OTRs for the prevention of NMSC includes systemic retinoids, nicotinamide and capecitabine. Retinoids are safe in OTRs but are generally reserved for those patients who are actively developing NMSC (e.g. >5 per year). Acitretin is the retinoid of choice, as a retrospective study showed that there was a significant reduction in SCC development for the first 3 years and three randomised controlled trials in OTRs have confirmed a significant reduction in actinic keratoses and/or SCC up to 2 years after transplant. To achieve effectiveness, chronic use is recommended, but there is a concern of rebound SCC with discontinuation [30].

Nicotinamide, a vitamin B3 analogue, enhances DNA repair and decreases ultraviolet-induced inflammation. Chen *et al.* [31] reported a reduced incidence of actinic keratoses by 13% and SCC by 30% in immunocompetent patients. An OTR study reviewing the use of nicotinamide versus placebo showed 88% partial resolution of actinic keratoses. In a recent randomised controlled trial in OTRs, nicotinamide was associated with a statistically non-significant reduction of NMSC and actinic keratoses [32]. However, nicotinamide is well-tolerated with minimal side-effects and is available over the counter. Further studies are needed in order to ascertain the effectiveness of nicotinamide in OTRs.

Capecitabine is an oral chemotherapy pro-drug that metabolises to 5-fluorouracil (5-FU). It has been used for chemoprevention in OTRs who develop more than two SCCs in 6 months or at least 10 new actinic keratoses within the past 12 months [33]. It is also used in OTRs with NMSC despite treatments with oral retinoids, photodynamic therapy (PDT), topical chemotherapies or after optimisation of immunosuppressive regimens. A case series showed that low-dose capecitabine significantly reduced the incidence of NMSC and actinic keratoses in OTR, with manageable adverse effects [34].

Treatment of Field Cancerisation in Transplant Patients

Field cancerisation with actinic keratoses and SCC *in situ* is a common problem in solid organ transplant patients and refers to the accumulation of genetic abnormalities in the tissue as a result of exposure to a particular carcinogen (Figures 1 and 2) [35,36]. These 'dysplastic fields' in the skin often arise as a consequence of chronic ultraviolet light exposure. Although there are limited data regarding the rate of progression from actinic keratoses/SCC *in situ* to invasive SCC, most agree that treatment of field cancerisation reduces the risk of invasive SCC and reduces patient mortality. Clearing the field cancerisation can also make it easier for dermatologists to examine the patient and more easily identify invasive SCC. In addition, field cancerisation

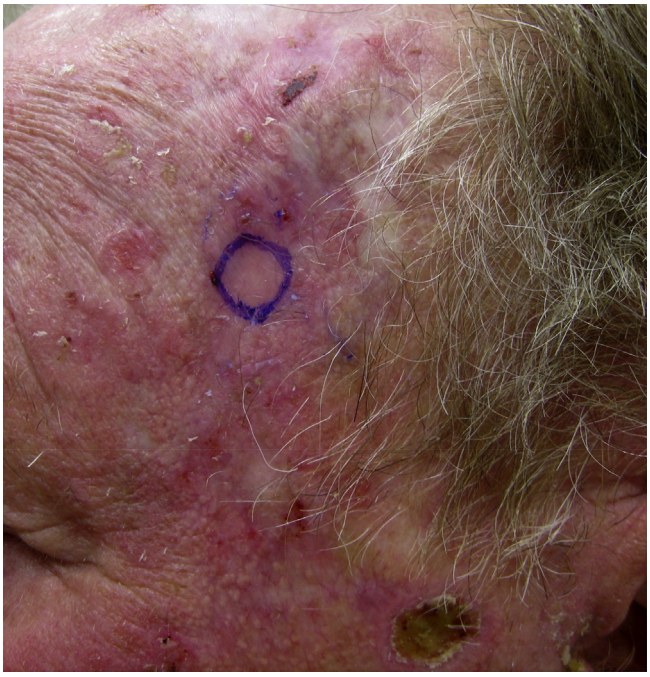

Fig 2. Squamous cell carcinoma and diffuse field cancerisation in a lung transplant patient.

often has a psychological impact on the patient as it can become disfiguring and also uncomfortable/painful. Topical 5-FU, imiquimod, PDT and cyclooxygenase inhibitors have all been investigated in transplant patients for the treatment of field cancerisation (Table 1). Given the diffuse nature of the disease, local destruction methods are usually ineffective and impractical [37].

Topical 5-fluorouracil

5-FU reduces the number of superficial NMSCs and actinic keratoses in organ transplant patients [35,38,39]. 5-FU inhibits thymidylate synthetase, which subsequently interferes with DNA synthesis and leads to cell death [35,40]. It is used either alone or in combination with α/β hydroxy acids or topical tretinoin to decrease the thickness of the stratum corneum and increase penetration. Ingham and Weightman [41] examined the safety and efficacy of 5-FU cream in renal transplant patients applied twice daily for 3 weeks and reported that 71% of patients had a 75% or greater clearance of actinic keratoses at 12 months after the initiation of treatment. The mean actinic keratoses clearance rate was 98% at week 8 and 79% at 12 months [41]. In addition, weekly application of chemowraps with 5-FU is a well-tolerated option for organ transplant patients with field cancerisation on the extremities. The topical 5-FU is applied in clinic, occluded with zinc-impregnated gauze and covered by a compression wrap and gauze bandages. The wraps are changed weekly in the clinic for 4 weeks [38,42,43]. Combination therapy is also becoming more frequently utilised for the treatment of field cancerisation in solid organ transplant recipients. Jambusaria-Pahlajani *et al.* [36] recently described four solid organ transplant recipients who had complete or nearly complete response to sequential treatment with curettage of hyperkeratotic actinic keratoses/SCC *in situ*, followed by application of topical 5-FU twice daily for 5 days, followed by blue light or red light PDT with 1-h incubation.

Topical Imiquimod

Topical imiquimod is an immunomodulatory agent that has both anti-tumour and anti-viral properties. It activates Toll-like receptor 7, which leads to the generation of various cytokines and mediators involved in the innate immune response [44]. Imiquimod is not as practical to treat field disease in transplant patients because of the small package size, which makes it difficult to use on large surface areas. In addition, there is a risk of cytokine release syndrome when imiquimod is applied over a large surface area [44]. However, studies have found imiquimod to be safe in transplant patients for treating skin areas of 60–100 cm^2 [45–47]. A recent randomised intra-individual controlled trial comparing imiquimod and PDT treatment in organ transplant patients found that PDT obtained a higher rate of actinic keratoses clearance at 3 months of follow-up and achieved shorter-lasting, but more intense, short-term skin reactions [48]. There are many treatment regimens that have been suggested in immunocompetent patients; however, the most effective treatment regimen has not yet been established in transplant patients. Additional studies are needed to determine the efficacy and risks of imiquimod in transplant patients.

Photodynamic Therapy

PDT induces photochemical apoptosis of dysplastic cells by creating reactive oxygen species. PDT also corrects abnormal cancer-associated gene expression and induces expression of dermal extracellular matrix genes in photo-exposed skin [49]. It is used to treat actinic keratoses, Bowen's disease and superficial BCC [50]. Multiple studies have shown PDT to be safe and effective in organ transplant patients [51]. It has not been shown to be associated with graft damage, even when large areas are being treated. PDT can be carried out in one treatment, with repeat treatments 1–4 weeks later, or cyclical PDT can be carried out in high-risk patients.

Topical Cyclooxygenase Inhibitors

Diclofenac is a non-steroidal anti-inflammatory agent that reduces the production of prostaglandins by inhibiting inducible cyclooxygenase-2 [38]. The typical dosing regimen is twice daily for 60–90 days and thus requires a motivated and compliant patient. Diclofenac 3% gel twice daily for 16 weeks led to a 41% clearance of actinic keratoses in organ transplant patients [52]. A recent series of 10 cases showed the effectiveness of a medical device containing piroxicam and SPF 50 + sunscreen filters in reducing actinic keratoses and improving field cancerisation in OTRs [53]. Piroxicam is structurally different from diclofenac and is a potent cyclooxygenase-1 inhibitor. Piroxicam also has the ability to induce apoptosis and suppress metalloproteinase 2 and 9 activities, which are associated with tumorigenesis [53]. The anti-viral properties of piroxicam may be relevant in transplant patients given the increased rate of β-HPV DNA associated with cutaneous SCC in immunosuppressed patients [54].

Treatment of Non-melanoma Skin Cancer in Organ Transplant Recipients

The treatment of NMSCs in OTRs is not all that different than the general population. The major difference in therapy is based on patients who have an extensive history of NMSCs.

SCCs in OTRs tend to be more aggressive when compared with the general population, not only with their subtypes, but also with treatment outcomes [55,56]. With any high-risk lesion or when tissue conservation is preferred, Mohs micrographic surgery is the recommended treatment. There is a lack of evidence suggesting that Mohs has a higher cure rate in immunosuppressed patients; however, there is a bevy of data to suggest that it has a higher cure rate in immune-competent patients. If tissue conservation is not paramount and the lesion is not considered high risk then

Table 1
Treatments indicated for field cancerisation in transplant patients

Treatment	Mechanism of action	Indications
Topical 5-fluorouracil	Pyrimidine analogue Inhibits thymidylate synthetase Interferes with DNA synthesis	Actinic keratoses Superficial BCC SCC *in situ* (off-label)
Topical imiquimod	Activates Toll-like receptor 7 Increases cytokine production and release Activates innate and acquired immune response	Actinic keratoses Genital warts Superficial BCC on trunk and extremities less than 2 cm SCC *in situ* (off-label)
Photodynamic therapy	Induces photochemical apoptosis of dysplastic cells by creating reactive oxygen species	Actinic keratoses Superficial non-melanoma skin cancers
Topical cyclooxygenase inhibitors	Reduce the production of prostaglandins by inhibiting cyclooxygenase Suppress metalloproteinase 2 and 9 Some have anti-viral properties	Actinic keratoses Osteoarthritis

BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

wide local excision can be carried out. Recommended margins range between 3 and 10 mm; recurrent and residual SCCs have not been studied with regards to optimal margins for excision in OTRs [57]. Despite the logic that immunosuppressed patients are at higher risk of infection, preoperative antibiotics have not been studied in transplant patients for whom surgery is indicated (Table 2).

Immunosuppressed patients are also at a higher risk for eruptive keratoacanthomas when compared with immune-competent patients [58] (Figure 3). Although there are no Food and Drug Administration-approved therapies for this entity, off-label medications include topical imiquimod, topical/intralesional 5-FU with or without zinc oxide wraps, intralesional bleomycin and intralesional methotrexate [59–61]. The safety of these intralesional therapies has yet to be determined in organ transplant patients. Systemic retinoids can be used to treat eruptive keratoacanthomas and also to reduce the risk of developing subsequent SCC. *In situ* lesions of SCC have not been studied in OTRs and there remains considerable dissent among practitioners as to whether destructive methods for treatment are as effective as surgery [40].

Radiation therapy is used in patients with inoperable tumours, incomplete resection, extensive perineural invasion or those who will be unable to tolerate surgery [56]. It is also important to remember that some patients will experience 'tumour fatigue', in which they have been afflicted by so many NMSCs that they no longer desire surgery. A large multi-institutional study investigating the effect of immune status on disease outcomes in patients with cutaneous SCC of the head and neck who underwent surgery and received postoperative radiation therapy found that despite receiving bimodality therapy with both surgery and postoperative radiation, immunosuppressed patients with cutaneous head and neck SCC had dramatically inferior outcomes compared with immunocompetent patients, including locoregional recurrence-free survival and progression-free survival. The study provides further evidence that the immune status is a strong prognostic factor and should be considered in treatment algorithms as well as staging systems [55]. In addition, it highlights the importance of clinical trials investigating the methods of intensified therapies for immunosuppressed patients. Most clinical trials exclude immunosuppressed patients in an effort to reduce heterogeneity, which has led to significant gaps in data-driven clinical guidelines. Given that it is well established that cutaneous SCCs in immunosuppressed patients tend to be more aggressive tumours, with higher rates of perineural invasion, lymphovascular invasion and higher recurrence rates, providers should consider offering immunosuppressed patients with earlier stage disease postoperative radiation. Wide radiotherapy field margins are recommended (4–5 cm) to include possible subclinical spread, which is frequently present in immunosuppressed patients [62]. Although radiation therapy can make surgical intervention in the future more difficult in the irradiated field, it is important to be aggressive with the treatment and use wide margins including the surrounding field cancerisation.

Table 2
Summary of the surgical procedures indicated for non-melanoma skin cancer in organ transplant recipients

Intervention	Indication
Mohs micrographic surgery	High-risk cutaneous SCC Conservation of tissue in SCC and BCC
Wide local excision	Normal-risk non-melanoma skin cancer, including keratoacanthomas
Destruction	Eruptive keratoacanthomas

BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Medical options for the treatment of advanced SCC have become available in the form of epidermal growth factor receptor (EGFR) inhibitors. Activation of EGFR in native tissue acts to induce cell proliferation, differentiation, migration, adhesion and inhibit apoptosis. EGFR inhibitors work on tumour cells by decreasing angiogenesis, invasiveness and metastatic spread via these mechanisms [63]. These include cetuximab and panitumumab. Cetuximab is

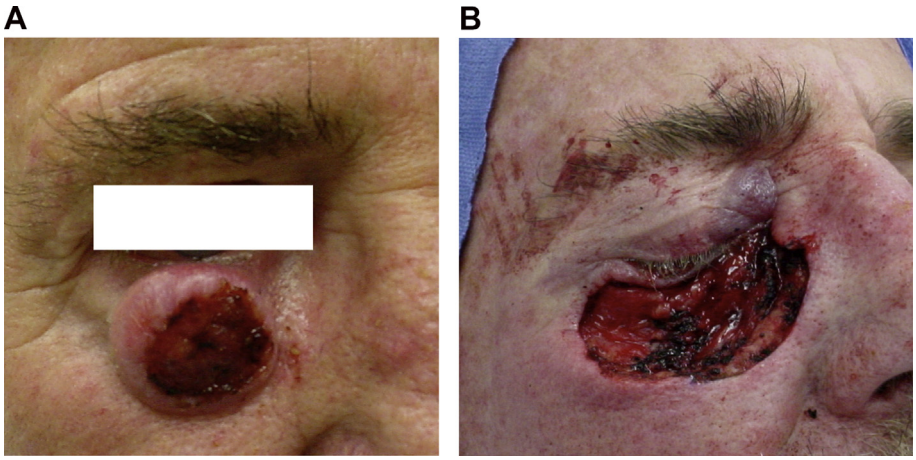

Fig 3. (A) Keratoacanthoma in a renal transplant patient and (B) surgical defect after Mohs micrographic surgery.

given as an intravenous infusion of 400 mg for the first treatment and 250 mg weekly thereafter. Panitumumab is also given as an intravenous infusion of 6 mg/kg every 2 weeks. EGFR inhibitors have a significant risk of cutaneous side-effects, with some authors citing as high as 90% of patients experiencing eruption, which seems to be mostly papulopustular. Evidence suggests that using high-potency topical steroids as a prevention of this side-effect carries a IB recommendation [64].

Cemiplimab, a PD-1 inhibitor, was recently approved for the treatment of metastatic cutaneous SCC or locally advanced cutaneous SCC in patients who are not candidates for curative surgery or curative radiation, but has not yet been studied in transplant patients. Although this may be a potential treatment in transplant patients in the future, it should be used with caution given the potential risk of graft rejection with PD-1 inhibitors.

Together with therapies for SCC in OTRs, systemic therapies have been developed for advanced BCC. These include smoothened inhibitors vismodegib and sonidegib. These medications inhibit the hedgehog pathway via smoothened antagonism. These therapies have significant incidence of muscle cramping and some experts recommend beginning L-carnitine as prophylaxis before initiation of these medications. Vismodegib has been used successfully in transplant patients, including patients receiving cyclosporine therapy. Further research is needed to evaluate the safety of the smoothened inhibitors in transplant patients on other immunosuppressive agents [65,66]. A summary of non-surgical interventions for high-risk NMSCs is detailed in Table 3 and is also further discussed under *Future Trends* below.

The Role for Modification of Immunosuppression

Adjusting the immunosuppressive regimen is an important adjuvant therapeutic strategy for managing skin cancers in transplant patients and requires integrated multidisciplinary care with the entire transplant team. Both the duration of immunosuppression and the type of medication affect a patient's risk of developing skin cancer. Immunosuppressive regimens can typically be decreased more aggressively in renal or liver transplant patients compared with cardiac and lung transplant patients; renal transplant patients have the option of returning to dialysis and there is a greater ability of liver tissue to recover if rejection occurs [67]. A mild reduction in immunosuppression should be considered once multiple skin cancers per year develop or with individual high-risk skin cancers. A moderate reduction should be considered when patients experience greater than 25 skin cancers per year or for skin cancers with a 10% 3-year risk of mortality. Severe reduction should be considered only for life-threatening skin cancers [67].

Mammalian target of rapamycin inhibitors (mTORi) have a protective effect on the development of NMSCs and have the ability to partially reverse the oncogenic effects of other immunosuppressive agents [68–70]. There is growing evidence suggesting the benefit of converting to mTORi to prevent subsequent cutaneous SCC after the first post-

Table 3
Summary of the non-surgical interventions and their indications in organ transplant recipients

Intervention	Indication
Radiation	Inoperable tumours Incomplete resection Extensive perineural invasion Unable to tolerate surgery Tumour fatigue/multiple tumours Recurrent tumours
EGFR inhibitors	Advanced SCC
Cemiplimab	Metastatic SCC Locally advance SCC (in patients who are not candidates for surgery or radiation)
Smoothened inhibitors	Locally advanced or metastatic BCC

BCC, basal cell carcinoma; EGFR, epidermal growth factor receptor; SCC, squamous cell carcinoma.

transplant skin cancer occurs [71,72]. There continues to be a lack of data regarding the benefit of starting an mTORi earlier, before the diagnosis of the first skin cancer.

Numerous studies have shown that mycophenolate mofetil may inhibit skin cancer development [73,74]. Switching to mycophenolate mofetil after at least 1 year of azathioprine treatment decreased the incidence of cutaneous SCC in lung transplant patients compared with continued use of azathioprine [75].

Discussion/Future Trends

Role of Human Papillomavirus Vaccination in the Prevention and Treatment of Squamous Cell Carcinoma

β-HPV DNA has been implicated in the development of cutaneous SCC in immunosuppressed patients and is detectable in >80% SCCs in OTRs; however, the role of HPV in SCC pathogenesis remains unclear. Current HPV vaccines target α-HPV types that cause cervical, anogenital and oropharyngeal cancers [76]. Until now, suboptimal responses have been shown on the immunogenicity of HPV vaccine in post-transplant patients [77]. Novel vaccines that could potentially offer cross-reactivity against β-HPV are being developed; this could offer a new avenue if found to be efficacious, especially if administered pre-transplantation [78].

It has been reported that a 90-year-old woman with multiple inoperable cutaneous basaloid SCCs was successfully treated with a combination of systemic and intratumoral administration of HPV vaccine. She had complete resolution at 11 months. Although this patient was not an OTR, reduced immunity is seen in the elderly [79].

The Future of Targeted Therapies

Immunotherapies have transformed melanoma care and may offer promising results in the management of NMSC. Potential pathways identified are the hedgehog pathway signalling inhibition for BCC and PD-1/PD-L1 inhibition for MCC or metastatic cutaneous SCC. The presence of higher PD-L1 expression in cutaneous SCC has been linked to higher grade, tumour thickness and risk of developing metastases [80]. PD-1/PD-L1 inhibition needs to be used cautiously as it has been associated with case reports of transplant rejection [81]. Cemiplimab is a PD-1 inhibitor; emerging data are showing efficacy in the treatment of metastatic SCC and there are currently trials in progress studying the effect on advanced BCC [82]. However, immunocompromised patients have been excluded from these trials. PD-1 inhibition is effective in treating MCC, as a recent study showed a response rate of 62% in Merkel cell polyomavirus-positive tumours with the use of pembrolizumab [83].

Anti-cytotoxic T-lymphocyte-associated protein-4 (anti-CTLA-4) has been shown to be efficacious in treating solid tumours in OTRs. Anti-CTLA-4 inhibitors are better tolerated without a suggestion of allograft rejection [84]. Interleukin-6 may play a potential role in Kaposi sarcoma pathogenesis. Therefore, the use of retinoic acid has been used in view of its effect on down-regulating interleukin-6 expression. Alitretinoin 0.1%, a topical retinoid, has been used in Kaposi sarcoma with responses in one-third to one-half of patients [85].

Conflict of interest

The authors declare no conflicts of interest.

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