Management of skin cancer in recipients of solid organ transplants

ABSTRACT

Recent improvements in post-transplant care have led to an increased life expectancy for recipients of organ transplants. These patients require lifelong immunosuppression, which is associated with an increased incidence of malignant disease. Skin cancers are the most common malignancies seen in recipients of organ transplants and are associated with significant morbidity and mortality. This review describes factors pertaining to the development and prognosis of skin cancers in recipients of organ transplants, as well as outlining prevention and management strategies in this cohort.

Skin cancer is the most common malignancy affecting white populations worldwide, and its incidence continues to rise (Perez et al, 2017). Owing to lifelong immunosuppression, recipients of organ transplants are at significantly greater risk of developing skin cancers than the general population. It is estimated that around half of Caucasian recipients of organ transplants will, at some point, develop non-melanoma skin cancer (Euvrard et al, 2003). Squamous cell carcinoma is the most common cancer, with an incidence 65–250 times greater in recipients of organ transplants than that in the general population (Perez et al, 2017). The second most common skin cancer, basal cell carcinoma, has a 10–16 times increased incidence in recipients of organ transplants, followed by melanoma and Kaposi sarcoma (Euvrard et al, 2003; Perez et al, 2017). The incidence of rarer skin cancers, such as Merkel cell carcinoma, is also significantly increased in recipients of organ transplants (Kearney et al, 2017).

Pathogenesis

The association between immunosuppression following solid organ transplantation and an increased risk of skin cancers was first described by Walder et al (1971). Proposed mechanisms to explain the increased risk include:

1. A reduction in immune surveillance, leading to increased survival and proliferation of abnormal cells (Krisl and Doan, 2017)
2. Direct carcinogenic effects of some immunosuppressive agents (Perez et al, 2017)
3. Oncogenic viruses, which can become reactivated in immunosuppressed patients (Krisl and Doan, 2017).

Risk factors

Similar to the immunocompetent population, fair skin, male sex and ultraviolet radiation remain significant risk factors for the development of non-melanoma skin cancer in recipients of organ transplants (Mittal and Colegio, 2017). Specific risk factors in those who have had an organ transplant include a pre-transplant history of skin cancer, older age at transplantation, and a greater degree and duration of immunosuppression (O'Reilly Zwald and Brown, 2011a; Harwood et al, 2013). Patients who develop squamous cell carcinoma after transplantation are also more likely to develop further non-melanoma skin cancer in future (Naldi et al, 2018). Transmission of skin cancers from donor to recipient has been reported, but the risk is extremely low (0.2%) (O'Reilly Zwald and Brown, 2011b).

Prognosis

Cancer is the second most common cause of death in recipients of organ transplants, behind cardiovascular disease (Alberú, 2010). Studies suggest a worse prognosis compared with the general population, with nearly nine times greater skin cancer-specific mortality in recipients of organ transplants (Garrett et al, 2016). Not only are such patients more likely to develop squamous cell carcinoma compared with immunocompetent individuals, but lesions tend to be more aggressive, and have higher recurrence rates and higher mortality (O'Reilly Zwald and Brown, 2011a). Similarly, recipients of organ transplants with malignant melanoma and Merkel cell carcinoma have more aggressive disease and a worse prognosis, with a mortality from post-transplant melanoma of four times that seen in the general population (O'Reilly Zwald and Brown, 2011a).

Immunosuppressive medication

Combination therapy, specifically 'triple therapy', has been the standard maintenance immunosuppressive regimen in kidney transplantation in the USA since the 1980s. Compared with older regimens, combination therapy has led to significant improvements in transplant rejection rates, tolerability and patient survival. Maintenance

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regimens today usually consist of a calcineurin inhibitor (tacrolimus preferred over ciclosporin), an antimetabolite (mycophenolate mofetil preferred over azathioprine) and corticosteroids (Chan et al, 2001; Kearney et al, 2017).

The overall level of immunosuppression is implicated in the development of skin cancers in recipients of organ transplants (O'Reilly Zwald and Brown, 2011a). Data on specific immunosuppressants are lacking, but ciclosporin and azathioprine are considered particularly high risk (Perez et al, 2017). Some evidence suggests that azathioprine, which is a direct photocarcinogen, carries the highest risk of skin cancer (Mittal and Colegio, 2017; Naldi et al, 2018). The newest class of agents, the mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, has been associated with a lower risk of skin cancer (Krisl and Doan, 2017). Unfortunately, the use of mTOR inhibitors is limited by frequent side effects including gastrointestinal upset, hyperlipidaemia, myelosuppression, oedema, mucositis and detrimental effects on wound healing. They have also been associated with graft failure and death in some studies (O'Reilly Zwald and Brown, 2011a; Blomberg et al, 2017; Kearney et al, 2017).

Although not an immunosuppressant, long-term use of voriconazole, a prophylactic antifungal frequently given to lung transplant recipients, has been associated with development of aggressive squamous cell carcinoma (Williams et al, 2014).

Primary prevention

Prevention of skin cancers in recipients of organ transplants requires a multidisciplinary approach, through close partnership between dermatologists, transplant teams and oncologists (O'Reilly Zwald and Brown, 2011b; Perez et al, 2017). In the UK, transplant teams provide skin care advice and skin examination (or at least inquiry) as part of regular transplant follow up, with referral of high-risk patients to dedicated dermatology clinics (discussed later). The key primary prevention strategies are summarized below.

Table 1. Recommended wait times before transplantation

Skin cancer history	Wait time after treatment
Premalignant lesions Basal cell carcinoma Low-risk squamous cell carcinoma Melanoma in situ or lentigo maligna	No wait necessary
High-risk squamous cell carcinoma (without nodal or metastatic disease)	2–3 years
Squamous cell carcinoma with local nodal disease (after lymph node dissection and radiotherapy)	5 years
Melanoma stages I–II Merkel cell carcinoma	2–5 years
Distant metastatic disease Melanoma stages III or IV	Not eligible for transplantation

modified from Zwald et al (2016)

Skin cancer screening and surveillance

Pre-transplantation, all patients should receive formal assessment with skin examination and palpation of lymph nodes. Any suspicious lesions should be excised and sent for pathological examination (Kearney et al, 2017). Risk factors should be carefully assessed to help determine follow-up frequency and, in the case of previous invasive skin cancer, wait time before transplantation. Aggressive treatment of premalignant lesions is strongly advised.

Patient education

Ongoing patient education, emphasizing the importance of photoprotection and regular skin self-examination, is also important (O'Reilly Zwald and Brown, 2011b). Ultraviolet exposure is the most important modifiable risk factor for the development of skin cancer in recipients of organ transplants (Mittal and Colegio, 2017). Daily sunscreen application reduces the incidence of actinic keratoses and squamous cell carcinoma in this group (Blomberg et al, 2017), with studies supporting the efficacy of promoting sun protection behaviours in transplant patients (Naldi et al, 2018).

Recommended photoprotection includes daily use of sunscreens (SPF 30 or higher, with ultraviolet A and B protection), sun avoidance between 11:00 and 15:00 hours, avoiding other exposure to ultraviolet radiation (such as tanning parlours), and wearing adequate protective clothing (long-sleeved shirts, broad-brimmed hats, sunglasses, long trousers) (Naldi et al, 2018). As sun avoidance increases the risk of vitamin D deficiency, supplementation should be considered (O'Reilly Zwald and Brown, 2011b).

Patients should be advised to perform monthly whole-body skin self-examinations (Kearney et al, 2017). Online patient information and tutorials on skin self-examination are available (American Academy of Dermatology, 2018).

Wait time

In patients with a history of invasive skin cancer, a delay before transplantation might be recommended, depending on the tumour type and stage, presence of high-risk features and available alternatives to transplantation. The International Transplant Skin Cancer Collaborative has published wait time recommendations based on skin cancer history (*Table 1*) (Zwald et al, 2016).

Immunosuppressive regimen

The choice of immunosuppressive regimen can influence the risk of post-transplant skin cancer; regimens with a lower overall level of immunosuppression and/or regimens including an mTOR inhibitor may be considered in patients who are at high risk of skin cancer with the aim of minimizing risk and prolonging the time to onset of non-melanoma skin cancer (O'Reilly Zwald and Brown, 2011a).

Management of premalignant lesions

Actinic keratosis

Actinic keratoses are very common and present as individual lesions or as field change at sun-exposed sites (Euvrard et

al, 2003; O'Reilly Zwald and Brown, 2011a). Not only are actinic keratoses more likely to progress to squamous cell carcinoma in recipients of organ transplants, but multiple hypertrophic actinic keratoses within field change can make it more difficult to identify squamous cell carcinoma (Mittal and Colegio, 2017). In recipients of organ transplants the risk of squamous cell carcinoma increases with the number of actinic keratoses, with >50 actinic keratoses being associated with a greater risk (Bouwes Bavinck et al, 2007).

Individual actinic keratoses are typically treated with local destructive therapies: cryotherapy, curettage and cautery, and occasionally carbon dioxide laser or with topical agents. For areas of field change, topical therapy with 5-fluorouracil, ingenol mebutate, imiquimod, photodynamic therapy or topical diclofenac are preferred (O'Reilly Zwald and Brown, 2011b).

Topical 5-fluorouracil is effective and commonly used, but use is limited by patient compliance as a result of the long treatment duration (3–6 weeks) and side effects relating to a predictable inflammatory reaction (Blomberg et al, 2017). Actikerall, a combination of 5-fluorouracil (0.5%) and salicylic acid (10%), is used to treat hyperkeratotic actinic keratoses. Treatment is required for up to 12 weeks (Simon et al, 2015).

Ingenol mebutate (Picato) is applied once daily for two to three consecutive days only. This is convenient for patients with impaired functional status where daily self-application for prolonged periods may be difficult (Anderson et al, 2009). A disadvantage is that treatment should be limited to small areas (up to 25 cm^2 at one time), making it less useful for treating field change.

There were initial concerns regarding the use of the immunostimulatory agent imiquimod in transplant patients, relating to a theoretical possibility of inducing immune activation and subsequent organ rejection. Studies suggest imiquimod is safe and effective in recipients of organ transplants when used for limited periods on small areas (O'Reilly Zwald and Brown, 2011b).

Photodynamic therapy is also effective in treating field change and may prevent new actinic keratoses and reduce progression to non-melanoma skin cancer in recipients of organ transplants. The main limitations of photodynamic therapy are pain, reduced efficacy compared to that in immunocompetent patients, as well as cost and resources (Wlodek et al, 2013; Mittal and Colegio, 2017). Topical diclofenac, ingenol mebutate and combination therapies of 5-fluorouracil and 10% salicylic acid also have limited evidence in the transplant population (Fleming et al, 2017).

Bowen's disease

The treatment of Bowen's disease, or squamous cell carcinoma in situ, in recipients of organ transplants is similar to that in immunocompetent patients. Common therapies overlap with those for actinic keratoses and include cryosurgery, topical 5-fluorouracil, curettage and cautery, and photodynamic therapy, as well as surgical excision (Mittal and Colegio, 2017).

Keratoacanthomas

Keratoacanthomas are difficult to distinguish from well-differentiated squamous cell carcinoma, both clinically and pathologically (Euvrard et al, 2003). Although these lesions can spontaneously regress, prompt treatment is recommended because of the diagnostic challenge (O'Reilly Zwald and Brown, 2011b). The mainstay of treatment is surgical: curettage and cautery for small lesions (<1 cm diameter) or excision (Blomberg et al, 2017). Topical treatments (5-fluorouracil and imiquimod) as well as intralesional injections (5-fluorouracil, methotrexate and bleomycin) have been reported but are not routine management.

Management of skin cancer

Squamous cell carcinoma

Any lesions suspicious for squamous cell carcinoma should be biopsied or directly excised for histological analysis (Mittal and Colegio, 2017). Primary squamous cell carcinomas in recipients of organ transplants are considered high risk because of the immunosuppression these patients receive; additional high-risk features include large size (>20 mm), high-risk histology (poorly differentiated, perineural invasion, deep), previous squamous cell carcinoma, high-risk location (ear, lip, over parotid gland, scalp, temple), and recurrence (Euvrard et al, 2003; O'Reilly Zwald and Brown, 2011b).

Curettage and cautery is used in carefully-selected lesions without additional high-risk features, or in patients with a large number of lesions who would not tolerate multiple surgical excisions (O'Reilly Zwald and Brown, 2011b). Three cycles of curettage and cautery are rapid, generally well tolerated, and less expensive than surgery. A significant disadvantage is the superficial depth of treatment and the lack of histological margin analysis (Mittal and Colegio, 2017).

Surgical excision with margin analysis is the preferred treatment of squamous cell carcinoma (Stratigos et al, 2015). For particularly high-risk lesions, or cosmetically-sensitive sites, Mohs micrographic surgery is the preferred technique, taking into consideration local training and resources. Mohs micrographic surgery has the highest reported cure rate (5-year cure rate >96%), but it is time-consuming and not universally available. If conventional surgical excision with postoperative margin examination is chosen, extended clearance margins of at least 6 mm beyond any surrounding erythema are recommended (Stratigos et al, 2015). Wound healing is often delayed in this population, secondary to steroid treatment (Kearney et al, 2017).

Management of high-risk squamous cell carcinoma should be undertaken as part of a specialist skin cancer multidisciplinary team. Some patients may require further investigation, including computed tomography, positron emission tomography, magnetic resonance imaging and rarely sentinel lymph node biopsy (Mittal and Colegio, 2017). Radiotherapy is reserved for non-

surgical candidates, or as adjunctive therapy for incomplete resections, recurrent squamous cell carcinoma (associated with higher risk of metastases), or in the presence of lymph node spread, extensive perineural involvement or metastases. In patients with advanced or inoperable disease, palliative radiotherapy may delay disease progression. Disadvantages of radiotherapy include increased risk of future skin cancers at treated sites, poor cosmetic result and possible increased difficulty in treating recurrences. Reducing immunosuppression should also be considered (O'Reilly Zwald and Brown, 2011b).

Management of metastatic disease is challenging in this population. Excision of involved nodal basins, radiotherapy and systemic chemotherapy is recommended, but evidence is limited (Mittal and Colegio, 2017). Studies on the use of immune checkpoint inhibitors, platinum-based chemotherapy and cetuximab have had controversial results. The lack of systemic treatment options for advanced and metastatic disease highlights the importance of close skin surveillance with early surgical excision (O'Reilly Zwald and Brown, 2011b).

Basal cell carcinoma

The management of basal cell carcinoma in recipients of organ transplants is similar to that in the general population. Surgical excision with 4–5 mm margins is the first-line treatment recommended by the British Association of Dermatologists (Telfer et al, 2008). High-risk basal cell carcinomas may require Mohs micrographic surgery; these include lesions around the eyes, nose, lips and ears, certain subtypes (morphoeic, infiltrative, micronodular and basosquamous), recurrent lesions, and those with perineural involvement (Telfer et al, 2008).

Curettage and cautery can be used for low-risk lesions. Cryotherapy is generally reserved for non-surgical candidates, for superficial basal cell carcinoma, or to reduce tumour size before surgery. For patients with multiple superficial lesions, topical imiquimod and photodynamic therapy can be used (Naldi et al, 2018). Radiotherapy can be considered for patients with high-risk disease who cannot tolerate surgery (Telfer et al, 2008), bearing in mind the disadvantages of radiotherapy discussed earlier.

Malignant melanoma

Malignant melanoma in recipients of organ transplants can be pre-transplant, de novo, post-transplantation (most common) or donor-derived (Mittal and Colegio, 2017). In the UK, malignant melanoma is managed by a specialist skin cancer multidisciplinary team. Following excisional biopsy, early stage melanoma is usually managed with wide local excision, based on the Breslow thickness. Sentinel lymph node biopsy is recommended for lesions stage II or stage IB with Breslow thickness >1 mm (National Institute for Health and Care Excellence, 2015). Reducing immunosuppression should be considered individually, based on staging and predicted transplant survival (Mittal and Colegio, 2017). In patients with lymph node involvement, the merits of lymph node dissection and/or adjuvant therapy are discussed. Additional staging studies, including positron emission tomography-computed tomography and magnetic resonance imaging, may also be considered in certain patients (O'Reilly Zwald and Brown, 2011b; National Institute for Health and Care Excellence, 2015).

For metastatic melanoma, prognosis is generally poor (Naldi et al, 2018). There are limited studies looking at melanoma-targeted therapies (BRAF inhibitors, MEK inhibitors) and checkpoint inhibition (inhibitors of PD-1 and CTLA-4) (Mittal and Colegio, 2017). Immunostimulatory therapies (such as interferon alpha) increase the risk of graft rejection, and decisions on their use are made on a case-by-case basis (O'Reilly Zwald and Brown, 2011b). Donor-derived melanoma usually presents with metastatic disease and has 72% mortality at a mean follow up of 30 months (Mittal and Colegio, 2017). Donor-derived melanoma is managed with cessation of immunosuppression, removal of the transplanted organ and targeted therapies (Naldi et al, 2018).

Other cancers

Kaposi sarcoma is a tumour of endothelial cell origin and is associated with human herpesvirus 8 (HHV8) infection (Euvrard et al, 2003). The main treatment is reduction or cessation of immunosuppression. Regression has been reported with discontinuation of immunosuppression or with changing from ciclosporin to sirolimus (Kearney et al, 2017). For isolated lesions, surgical excision, radiotherapy, cryotherapy or laser therapy may be considered. Local therapies, including topical retinoids, imiquimod and intralesional chemotherapy, have also been used. For persistent tumours with systemic involvement, options include chemotherapy with doxorubicin, vinblastine, paclitaxel, etoposide or bleomycin (Mittal and Colegio, 2017). The use of antivirals against HHV8, in HIV-negative recipients of organ transplants, is controversial (Euvrard et al, 2003).

Merkel cell carcinoma is a rare and aggressive skin cancer of neuroendocrine origin. Staging with positron emission tomography-computed tomography and sentinel lymph node biopsy helps guide management. Wide surgical excision or Mohs micrographic surgery are treatments of choice for the primary lesion. Adjuvant radiotherapy is generally recommended (O'Reilly Zwald and Brown, 2011a; Kearney et al, 2017). Lymph node dissection and adjuvant chemotherapy may be considered for lymph node involvement or metastatic disease (Mittal and Colegio, 2017). Reduction in immunosuppression has led to temporary and partial regression in several patients, but further research is needed (Kearney et al, 2017).

Primary cutaneous post-transplant lymphoproliferative disorders (PTLD) are rare. They include cutaneous T cell lymphomas, such as mycosis fungoides, and the rarer cutaneous B cell lymphomas. Management consists of reduction of immunosuppression in combination with topical therapies (corticosteroids) and/or superficial

radiotherapy. For more advanced disease, systemic immunomodulatory and chemotherapy are also considered (Seçkin et al, 2013).

Secondary prevention

It is widely recommended that patients attend dedicated 'transplant patient skin clinics'. In the UK, recipients of organ transplants who develop pre-malignant or cancerous skin lesions should be referred to dedicated clinics at their transplant centre or local hospital. This was formalised in the 'Improving outcomes' skin cancer guidance published by the National Institute for Health and Care Excellence (2006). The use of new tools, such as apps or teledermatology, should be assessed. These could be useful for providing education and for consultations by photo, especially for patients living in remote areas (Naldi et al, 2018).

Follow up

Recipients of organ transplants should be followed up regularly, with complete skin examinations and palpation of lymph nodes. The frequency of follow up will depend on skin type, photodamage, age at transplantation, and previous malignant and pre-malignant skin lesions (Harwood et al, 2013).

Modulation of immunosuppression

Observational studies demonstrate that a reduction in immunosuppression, including dose reduction, discontinuation of one agent in multiple-agent regimens, or changing regimens (e.g. from a calcineurin inhibitor to an mTOR inhibitor, or conversion from azathioprine to mycophenolate mofetil), may be beneficial in reducing further skin cancer development (Blomberg et al, 2017; Krisl and Doan, 2017). Reduction of immunosuppression should be considered in patients with multiple (>5) squamous cell carcinomas and patients with recurrent or metastatic disease. As reduction in immunosuppression may increase the risk of graft rejection, the individual risks and benefits must be carefully evaluated by the transplant team (O'Reilly Zwald and Brown, 2011b).

Chemoprevention

Chemoprevention regimens aim to delay or reduce the development of further skin cancers in recipients of organ transplants. They should be considered in patients with multiple (≥5) non-melanoma skin cancers, extensive actinic keratoses, aggressive and high-risk non-melanoma skin cancer, accelerated development of squamous cell carcinoma, eruptive keratoacanthomas, or squamous cell carcinoma with a history of lymphoma or leukaemia (O'Reilly Zwald and Brown, 2011b; Perez et al, 2017). Although studies support their efficacy, use is limited by tolerability and lack of evidence in the transplant population. Chemoprevention regimens primarily include systemic retinoids, although nicotinamide is becoming more widely available and there is emerging evidence for capecitabine.

Oral retinoids, particularly acitretin, are used for the secondary prevention of actinic keratoses and non-melanoma skin cancer. The use of acitretin is limited because of its side effects, including skin dryness and peeling, liver function abnormalities, musculoskeletal problems and dyslipidaemia. Owing to the 2-year post-treatment period of teratogenicity, use is avoided in women of childbearing potential; isotretinoin with a shorter wash-out period is preferred in this context. Acitretin effectively reduces the incidence of non-melanoma skin cancer during its use, but there is a rebound increase in lesions on cessation; it should therefore be considered a long-term therapy (Harwood et al, 2005). To improve tolerability, retinoids should be started at low doses (Naldi et al, 2018). More studies are needed to assess the long-term safety, efficacy and optimal treatment regimens.

Nicotinamide (vitamin B3) 500 mg twice daily may also be effective and is generally well tolerated. One randomized trial in immunocompetent patients with a history of non-melanoma skin cancer reported that nicotinamide reduced the incidence of further non-melanoma skin cancer (Naldi et al, 2018). Although data on recipients of organ transplants are limited, a phase II study in renal transplant patients (n=22) showed non-significant reductions in basal cell carcinoma and actinic keratoses (Chen et al, 2016). Concerns have been raised regarding an increased risk of infection and the number of aggressive tumours in this study, but the study was not powered to assess this and further research is required (Yélamos et al, 2017).

Early reports have shown that low-dose capecitabine, an oral chemotherapeutic agent, may decrease development of new cutaneous actinic keratoses, basal cell carcinoma and squamous cell carcinoma in recipients of organ transplants with a history of skin cancer. However, its side effects limit its use and further study is required (Jirakulaporn et al, 2011).

Conclusions

Skin cancer is a major cause of morbidity and mortality in recipients of organ transplants. Owing to inherent risk factors, including immunosuppression, skin cancers in this cohort are generally more severe and have a worse prognosis than those in the general population. Primary prevention through a proactive, multidisciplinary approach is therefore critical. It includes close skin cancer surveillance, patient education, and aggressive treatment of premalignant lesions. If recipients of organ transplants develop skin cancer, management should be tailored to this population and secondary prevention should be considered. This includes more frequent follow up, modulation of immunosuppressive therapy, and consideration of chemoprevention regimens. **BJHM**

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KEY POINTS

- Recipients of solid organ transplants are at a significantly higher risk of developing skin cancer than the general population.
- Regular screening in specialized clinics is recommended, with full skin assessment and, where appropriate, early and aggressive treatment of pre-malignant and malignant skin lesions.
- Ultraviolet exposure is the most important modifiable risk factor for the development of skin cancer. Meticulous photoprotection, sun avoidance and vitamin D supplementation are therefore recommended.
- Squamous cell carcinoma is the most common cutaneous malignancy in recipients of solid organ transplants, with a higher risk of recurrence, metastasis and overall mortality compared to immunocompetent individuals.
- Reduction in immunosuppression and chemoprevention regimens have a role in the management of aggressive or recurrent skin cancers in this population.

cancer/learn-about-skin-cancer/detect

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