FEATURE ARTICLE

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# Critical Facts About Transplant Dermatology

Alina Goldenberg, Sharon E. Jacob

**ABSTRACT:** This article is intended to provide a foundation for anyone interested in learning more about transplant dermatology. Herein, we present an organ-transplant-related, skin-cancer focused review with information on the epidemiology, pathophysiology, risk factors, treatment and management foci, prevention options, associated conditions, and future goals.

**Key words:** Epidemiology, Organ Transplant Recipient, Photoprotection, Skin Cancer, Treatment

Organ transplant recipients (OTRs) are faced with the bittersweet reality of having survived a transplantation only to be now faced with a significantly increased risk of developing skin cancer. The very medications that induce immunosuppression and allow the transplanted organ to survive also decrease the patients' ability to defend against skin cancer. In most cases, skin cancer can have a successful intervention and cure if recognized early. Depending on a constellation of other factors such as duration of immunosuppression, history of sun exposure, and previous history of skin cancer, some patients will suffer minimally from skin cancers. Others, however, have the misfortune of having hundreds of skin cancers, some of which may be aggressive and lethal. Herein, we present critical informational points regarding transplant patients' care and management within dermatology.

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## EPIDEMIOLOGY OF SKIN CANCER IN OTRS

Cutaneous malignancies are the most common cancers affecting OTRs (Berg & Otley, 2002). The risk of developing skin cancer increases from 7% after 1 year of immunosuppression, to 45% after 11 years, and up to 70% after 20 years as a result of intense, ongoing immunosuppressive regimens (Bouwes Bavinck et al., 1996). OTRs have a 65-fold increased incidence of squamous cell carcinoma (SCC) than the general population (Berg & Otley, 2002). In contrast to what is seen in the general population, among OTRs, SCCs predominate over basal cell carcinomas (BCCs) at a 4:1 ratio (Euvrard, Kinitakis, & Claudy, 2003). In addition, OTRs also have a twofold-to-fivefold increased risk of developing melanoma (Lévêque et al., 2000) and a 60-fold increased risk of developing Kaposi's sarcoma (Engels et al., 2011).

Importantly, SCCs in OTRs tend to be more aggressive, with higher rates of metastases than those in the general population (Buell, Hanaway, Thomas, Alloway, & Woodie, 2005; Euvrard et al., 2003). These aggressive SCCs often have accelerated growth (Euvrard et al., 2003), a high rate of recurrence in estimated 13.4% of patients (Winkelhorst, Brokelman, Tiggeler, & Wobbes, 2001), and metastasis in 5%–8% of patients (Martinez et al., 2003). Histologically, more aggressive lesions present with poor differentiation, a higher thickness (greater than 5 mm), and deeper invasion of tissues such as the muscle and bone (Cooper & Wojnarowska, 2002). These values are significantly higher than in the general population in which the case fatality rate because of any nonmelanoma skin cancer is considered to be 1% (Clayman et al., 2005) and metastasis approximated to be only 2% (Carucci et al., 2004). Thus, skin cancer risk among OTRs is a significant contributor to morbidity and mortality within this group.

## PATHOPHYSIOLOGY OF SKIN CANCER IN OTRS

The reason behind increased cutaneous carcinogenesis in OTRs is multifactorial. The required immunosuppressive

lifelong regimens limit patients' ability to fight skin cancer. Although the immunosuppressive medications protect the transplanted organ from rejection, they increase the risk for carcinogenesis via immune system impairment. Most immunosuppressive drugs act nonselectively resulting in a general limitation on the cell-mediated and humoral immunity, resulting in decreased surveillance capabilities and response time. This immunodeficiency state leaves the host susceptible to infections and, most importantly, cancer via uninhibited tumor cell proliferation and carcinogenesis. In addition, immunosuppressive medications have inherent carcinogenic potential and, thus, independently increase neoplastic risk. The patients' individual characteristics, including a history of viral infections and genetic risk factors, also contribute to their high rates of skin cancer (Guba, Graeb, Jauch, & Geissler, 2004; Marshall et al., 2000; Ramsay et al., 2003).

## RISK FACTORS FOR SKIN CANCER AMONG OTRS

In addition to the common pathophysiologic components for neoplasms present in all OTRs, certain risk factors hold more importance in the development of skin cancer. Duration of immunosuppression is one of the most important risk factors with a reported odds ratio (*OR*) of 1.164 (Ramsay et al., 2003). Male OTRs have 1.5 higher odds of developing SCC than female OTRs. Overall, OTRs with fair skin and red hair (Fitzpatrick skin type 1) have 8 and 4.4 times, respectively, the odds of having SCC posttransplant. Presence of 1–10 precancerous actinic keratoses (AKs) before transplant has an *OR* of 2.5 for the developing of skin cancer, and that *OR* increases to 11.7 if 10–100 AKs are present and to 59.8 if over 100 AKs are present (Ramsay et al., 2003). Advanced age at transplant is also associated with increased risk for skin cancer. Previous history of either BCC or SCC increases the odds for either skin cancer posttransplant (24.8 odds of developing secondary SCC and 8.7 odds of developing secondary BCC; Ramsay et al., 2003). Cumulative sun exposure increased the odds of SCC by 1.060 (Ramsay et al., 2003).

Interestingly, the type of immunosuppressive regimen used has had differing findings, as some studies report no significant difference in the odds of posttransplant skin cancer, suggesting that the inherent medication properties may not be as important as the overall long-term regimen (Ramsay et al., 2003). This theory is supported by evidence that patients treated with any three-drug regimen versus any two-drug regiment had two-to-three higher rates of nonmelanoma skin cancer (Glover, Deeks, Raftery, Cunningham, & Leigh, 1997). However, other studies show that the risk of skin cancer is lowest with combination of mycophenolate mofetil and sirolimus and highest with the combination of azathioprine and cyclosporine (Einollahi et al., 2010).

Smoking has been a controversial risk factor for skin cancer development among OTRs. Multiple studies have failed to show the association between smoking and the development of SCC (Foote et al., 2001; Frieling, Schaumberg, Kupper, Muntwyler, & Hennekens, 2000; Odenbro, Bellocco, Boffetta, Lindelöf, & Adami, 2005), whereas other studies showed moderate increase in risk (Grodstein, Speizer, & Hunter, 1995; Karagas et al., 1992; McBride, Olsen, & Green, 2011). Thus, further research is necessary to elucidate the relationship between cigarette use and skin cancer development among OTRs.

The type of organ that was transplanted has been found to be significant in the determination of skin cancer risk. The risk is greatest in patients who have received a double pancreas and kidney transplant (suggesting that an increased immunosuppressive load is important). Of patients who received a single organ transplant, the heart transplant patients have the highest risk, whereas liver transplant patients have the lowest. The reasons for this are unclear (Jensen et al., 1999; Perera, Child, Heaton, O'Grady, & Higgins, 2006; Wisgerhof et al., 2009).

## TREATMENT OF SKIN CANCER IN OTRS

The management of skin cancer among OTR patients is variable and individual dependent. Generally, treatment of precancerous lesions and skin cancer among OTRs does not differ from that in nonimmunosuppressed patients. However, because many OTRs develop numerous AKs over wide areas, topical chemotherapeutic agents such as 5-fluorouracil, imiquimod, or photodynamic therapy may also be used. For diagnosed SCC or BCC, cryotherapy, electrodessication and curettage, Mohs surgery, and excision may all be used (Maley & Olasz, 2014).

## FOLLOW-UP OF OTRS WITH SKIN CANCER

For OTR, regular follow-up with a dermatologist is essential. If no prior history of skin cancer exists, a yearly visit is deemed sufficient; however, if there are increased risk factors or history of skin cancer, visits must be more frequent—within intervals ranging from 3 to 6 months (Harwood et al., 2013).

## PREVENTION OF SKIN CANCER IN OTRS

Prevention of skin cancers in OTRs is a difficult task but one that must be addressed in a multifactorial way. Primary prevention via education regarding sun protective strategies is vital. A 2006 randomized controlled trial compared standard episode-of-care-based education with intense repetitive written education about skin cancer after organ transplant based on performance on self-administered assessment tools after the education. The study reported that the participants who received the intense educational session were more adherent to sun protective behaviors at 3 and 10 months after the intervention (Clowers-Webb et al., 2006). Thus, photoprotection should be advised to all OTRs, which includes sun avoidance during peak hours between 10 A.M. and 3 P.M., covering the scalp and exposed skin areas with hats, wearing SPF clothing, using sunscreens, and doing regular self-skin checks (Goldenberg, Nguyen, & Jiang, 2014).

However, OTRs with a history of skin cancer may require additional therapeutic measures to reduce their risk

of new tumors. For example, tapering of their immunosuppressive regimen may be recommended for some patients (Berg & Otley, 2002; Otley, Coldiron, Stasko, & Goldman, 2001). If patients experience more than five-to-six new SCCs per year, chemoprevention with low-dose oral retinoids (e.g., acitretin) or low-dose oral capecitabine may be used, as these medications help minimize the incidence of new lesions (Chen, Craig, & Shumack, 2005; Endrizzi, Ahmed, Ray, Dudek, & Lee, 2013). However, retinoids must be used cautiously as they may often cause unwelcomed side effects such as pruritus, xerosis, arthralgias, and hyperlipidemia (Euvrard et al., 2003). Thus, topical retinoids and topical calcineurin inhibitors such as tacrolimus or pimecrolimus may be considered (Rook & Shapiro, 2001; Stockfleth, Ulrich, Meyer, & Christophers, 2002).

## INFECTIOUS DISEASE

As in the pathogenesis of neoplasms, impairment of immune system surveillance predisposes OTRs to a variety of cutaneous infections. Dermatophyte and yeast infections occur most frequently, followed by herpes simplex and zoster viruses and bacterial infections (Hogewoning et al., 2001). Opportunistic infections often occur at later stages of immunosuppression approximately after 5–6 months of treatment (Maley & Olasz, 2014). It is important to note that immunosuppressed patients often present with unusual clinical manifestations of common and opportunistic infections because of the severe level of immune system inhibition. A low threshold must be present for evaluation of OTRs for deep infections and necrotizing fasciitis, especially at their surgical sites (Lipworth, Saavedra, Weinberg, & Johnson, 2012).

## UNIQUE RISK FOR OTRS: GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease most frequently occurs after hematopoietic stem cell transplant but has been reported to occur in 5.6% of small intestine transplant patients and 1%–2% of liver transplant patients (Mazariegos et al., 2004; Taylor, Gibbs, & Bradley, 2004). Signs and symptoms often begin 2–6 weeks after transplant and may mimic a drug eruption with a morbilliform-like rash and desquamation. As mortality because of graft-versus-host disease may be greater than 75%, a high index of suspicion is essential in all clinicians treating OTRs (Kohler et al., 2008).

## "WHOLE-PATIENT" APPROACH FOR OTRS

OTRs are complex patients who require a "whole-patient" approach to care, which includes mind, body, and spirit treatment. In addition to management of OTR patients' physical issues, it is imperative that dermatology providers also address their patients' overall psychological and spiritual well-being. A holistic mind–body–spirit approach has been used in a number of conditions including cancer and human immunodeficiency virus to improve well-being, decrease stress and anxiety, and increase positive emotion (National Cancer Institute, 2014). Specifically, yoga has been shown to be effective in managing stress and stress-induced disorders as well as increasing relaxation and improving mood (Bowman et al., 1997; Mandanmohan, Jatiya, Udupa, & Bhavanani, 2003; Parshad, 2004; Taneja, 2014; Vempati & Telles, 2002). As such, negative emotions may hinder treatment adherence and overall disease improvement. Addressing these issues head on and evaluating patients' needs for referrals to other services such as yoga are essential parts of OTR patient management.

## FUTURE GOALS: EARLY SURVEILLANCE

Overall, although eradication of skin cancer risk among OTRs would be an ultimate goal, it is not a feasible approach. Thus, at this time, the focus must be on secondary prevention via the promotion of sun protection education and use of chemopreventive "field" (regional area) treatments and tertiary prevention via timely treatment of skin cancer lesions. ■

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