Journal of Photochemistry and Photobiology B: Biology 101 (2010) 150–159

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology B: Biology

journal homepage: www.elsevier.com/locate/jphotobiol

Dermatologic management, sun avoidance and vitamin D status in organ transplant recipients (OTR)

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ARTICLE INFO

Article history:
Received 2 November 2009
Received in revised form 15 February 2010
Accepted 1 April 2010
Available online 11 April 2010

Keywords:
Cancer protection
Organ transplant recipients
Skin cancer
Solar UV-exposure
UV-protection
Vitamin D deficiency

ABSTRACT

It is well known that skin cancer, especially cutaneous squamous cell carcinoma (SCC), in organ transplant recipients (OTRs) has higher incidence rates, behaves more aggressively and has higher rates of metastasis. OTRs who have been treated for many years with immunosuppressive medication are at the highest risk for developing malignant skin tumors. Protection against solar and artificial UV-radiation is crucial to prevent skin cancer in OTRs. However, investigations have revealed that solar UV-B-exposure and serum 25(OH)D levels positively correlate with decreased risk for various internal malignancies (e.g. breast, colon, prostate, and ovarian cancer) and other severe diseases. Therefore, it is important to detect and treat vitamin D deficiency in OTRs. This review discusses guidelines for the optimal management of these patients, that require communication between the transplant teams, the treating dermatologist and other clinicians.

1. Introduction

There is a high need in developing guidelines of care for organ transplant recipients (OTR) for these patients represent an increasing and significant challenge to clinicians including dermatologists. During the last decades, the annual numbers of performed solid organ transplants have been continuously increasing world-wide. As the United Network for Organ Sharing reported, over 25,000 solid organ transplantations were performed in 2003 In the United States of America (US) alone (based on OPTN data as of January 1, 2004) [1]. OTR have an increased risk to develop malignancies, with skin cancer representing the most common malignancy [2]. Moreover, OTR in general develop a more aggressive form of these malignancies. In consequence, dermatologic surveillance is of high importance for OTR, and these patients represent an increasing and significant challenge to clinicians including dermatologists. In OTRs, patient and organ survival have increased remarkably over the past three decades as a result of better immunosuppressive regimens and better post-transplant care. However, it now has become evident that the more effective immunosuppression regimens have as severe and unintended consequence resulted in more frequent and aggressive skin cancers [3–6]. It is well known that solar and artificial UV-exposure both before and after organ transplantation increase the risk to develop skin cancer and that the incidence of skin cancer increases with survival time after transplantation [3]. The biological behaviour of these malignant skin tumors reveals a much more aggressive profile when compared to the non-immunosuppressed population, leading to considerable cutaneous morbidity, mortality and decrease in quality of life.

2. Solid organ transplant recipients: a high-risk group with increased incidence and prevalence of nonmelanoma skin cancer (NMSC)

Nonmelanoma skin cancer (NMSC), most importantly basal cell carcinomas (BCC) and cutaneous squamous cell carcinomas (SCC) is the single most commonly diagnosed malignancy in the Caucasian population. In the US alone, an estimated 1 million new cases are reported annually [7]. Cutaneous SCCs are in general easily managed in immunocompetent patients where they rarely grow aggressively or metastasize. However, when SCCs develop in individuals who have been immunosuppressed over long time periods (e.g. in solid OTRs), they grow aggressively and represent a difficult clinical management problem with substantial morbidity and mortality. The clinical characteristics of different types of skin cancer in solid organ transplant recipients are summarized in Table 1. We know today that NMSC accounts for appr. 90% of all skin cancers in transplant recipients [8–10]. SCC represents the most common skin cancer in transplant recipients, occurring up to 250 times as frequently as in the general population [10]. The incidence of BCC is increased by a factor of appr. 10 in solid OTRs [10]. It has been shown that following transplantation, the usual BCC/SCC ratio in the general population (4:1 in higher latitude, respectively

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doi:10.1016/j.jphotobiol.2010.04.001

Table 1
Clinical characteristics of different types of skin cancer in solid organ transplant recipients.

	Incidence	Growth pattern	Metastatic behaviour	Special considerations for therapy
Malignant melanoma (MM)	2–8-fold increased incidence as compared to the general population	More aggressive as compared to the general population	More aggressive as compared to the general population	Sentinel lymph node biopsy may be useful for MM that are more than 1 mm thick or that are ulcerated In patients with metastatic MM, reduction or discontinuation of immunosuppressive medication should be considered
Basal cell carcinoma (BCC)	Incidence increased appr. by a factor of 10 as compared to the general population	More aggressive as compared to the general population	None	BCC can be treated with various therapeutic modalities, including Electrodessication and curettage (ED&C), surgical excision, or Mohs' surgery depending on the size of the lesion, its location and whether it is recurrent. Topical imiquimod for superficial BCC has been reported in a limited number of cases, but preliminary results are encouraging.
Squamous cell carcinoma (SCC)	Incidence increased appr. by a factor of 250 as compared to the general population. Develop at younger ages, starting in general 3–5 years after transplantation.	More aggressive as compared to the general population. Can be divided in low and high risk SCCs. High frequency of local recurrence (13.4%) during the first 6 months after excision	More aggressive as compared to the general population. Remarkably high frequency of lymph node metastasis (7%) during the second year after excision. Metastatic SCCs are characterized by poor prognosis with a 3-years disease specific survival of 56%	Any lesion suspicious for SCC should be biopsied or excised. Electrodessication and curettage (ED&C) may be performed at the time of biopsy for those lesions that are clinically determined to be less aggressive. For lesions judged to be low risk, treatment options include: cryosurgery with curettage, ED&C, surgical excision, or Mohs' micrographic surgery. Aggressively growing SCC should be treated with excisional techniques, particularly Mohs' micrographic surgery, surgery with intraoperative frozen section evaluation, or excision with postoperative margin assessment. Margins should include the subcutaneous fat and 6–10 mm beyond any surrounding erythema. If there is evidence of perineural involvement, invasion of surrounding bones or glands, unclear margins, or if the lesion persists after excision, then further evaluation is necessary. Radiation therapy should be considered in cases where there is perineural involvement or where there is inability to achieve clear margins. Sentinel lymph node biopsy (SLNB) should be considered for patients with high risk SCC. The decision to decrease immunosuppressive therapy should be discussed with the patient's transplant team. Any patient with metastatic nodal spread should be evaluated for excision with therapeutic lymphadenectomy or primary radiation therapy (XRT). Patients with in-transit cutaneous metastasis who do not have lymph nodes that are positive for metastatic spread should have excision of the primary and satellite lesions. In these patients, Mohs' surgery is recommended. Chemotherapy, the use of systemic retinoids, and the reduction of immunosuppressive medication are additional options that should be considered in patients with nodal spread or satellite lesions

2.5:1 in lower latitude) [11] reverses in favor of SCC up to rates >3:1 [12]. These differences are at least in part caused by differences in genetic backgrounds, skin types and sun exposure habits at different latitudes [13].

In recent yeas, it has been demonstrated that the incidence of NMSC increases continuously with the duration of the time period after transplantation and with the level of immunosuppression. Additionally, it has been shown that solar and artificial UV-exposure both before and after organ transplantation increase the risk to develop skin cancer and that the incidence of NMSC varies with the type and dose of immunosuppressive medication used. It was reported that in Australia, NMSCs occur in appr. 3% of renal transplant recipients by 1 year post-transplantation, in appr. 25% by 5 years, and in appr. 44% by 9 years after transplantation [14]. Patients from the Netherlands, United Kingdom, and Italy were shown to have a 10–15% incidence of skin cancer 10 years after solid organ transplantation. In the United States, a study from Oregon reported a 35% incidence of skin cancer 10 years post-transplantation [15].

Several independent pathogenetic mechanisms that involve the cutaneous immune system were discussed to be responsible for these clinical findings, including dysfunction of antigen presentation, induction of immunosuppressive cytokines (e.g. IL-10, TNF-α), isomerization of trans-urocanic acid to cis-urocanic acid and formation of reactive oxygen species [15,16].

3. An underrecognized clinical challenge: the aggressive behaviour of nonmelanoma skin cancer in transplant recipients

The biologic behaviour of cutaneous SCC, including local growth and metastasizing behaviour, is more aggressive in solid OTRs as compared to the general population. In OTRs, SCCs develop at younger ages, in general starting 3–5 years after transplantation. In OTRs, SCCs also reveal a more aggressive behaviour, with a high frequency of local recurrence (13.4%) during the first 6 months after excision and with a remarkably high frequency of lymph node metastasis (7%) during the second year after excision [17]. In OTRs, these tumors in general grow rapidly to a relatively large size (>2 cm diameter) and develop an aggressive histological growth pattern (Broders grade 3 or 4), that is often associated with perineural invasion or invasion of cartilage, fat, or bone [17]. Metastatic SCCs are characterized by poor prognosis with a 3-years disease specific survival of 56% [17]. Patients with a history of NMSC prior to transplant are at an increased risk of metastatic NMSC, most likely because of genetic factors. As long-term survival after organ transplantation is increasing, partly because of better immunosuppressive regimens and post-transplant care, dermatologists including dermatologic oncologists will continue to be challenged in guaranteeing the optimal care of potentially life threatening NMSC in the post-transplant period [18].

4. Risk factors for the development of nonmelanoma skin cancer in transplant recipients

Several risk factors have been identified that lead to an increased risk of NMSC in transplant patients. Some of these risk factors, such as Fitzpatrick skin types I or II, significant exposure to ultraviolet (UV) radiation, and age lead to an increased risk of NMSC both in the general population and in OTRs [19,20]. Other important risk factors, including type, dosage, and duration of immunosuppressive medication, are more specifically associated with the OTR population. Patients with a history of melanoma or NMSC are at higher risk to develop aggressive and potentially life-threatening skin cancer post-transplantation. Penn et al. found that 62% of OTRs who had a history of NMSC developed additional NMSC after transplantation [21]. They also noted that 30% of OTRs who had malignant melanoma developed melanoma metastases and subsequently died from metastatic melanoma [21]. In OTRs, the presence of an increased number of actinic keratoses (AK) is also associated with a higher risk of developing NMSC [22]. It has to be emphasized that the management and treatment of AKs is of high importance in OTRs. Other important risk factors that are associated with the development of skin cancer after transplantation are the level and the duration of immunosuppression. More intensive and longer regimens lead to an increased risk for the development of AKs and skin cancer [8,23–25]. Infection with human papillomavirus (HPV) may be another risk factor for the development of NMSC, especially in OTRs and other immunosuppressed patients. It has been speculated that cutaneous infections with HPV types 5 and 8 (HPV5, HPV8) may cause an increased risk for NMSC development in transplant recipients [26]. Local and systemic immunodeficiencies in general promote the proliferation and activity of HPV, which acts as a cocarcinogen. Therefore, the presence of HPV-induced verrucous lesions in OTRs is associated with an increased risk of NMSC. Recent studies have shown the presence of HPV DNA in up to 70–90% of cutaneous SCCs [23,24,27,28]. The incidence of HPV in AKs and NMSC has also been shown to be increased in OTRs as compared to non-immunosuppressed patients [29,30]. It has now been demonstrated that heart transplant recipients are at the greatest risk to develop skin cancer post-transplantation, followed by kidney and liver transplant recipients. It is known that recipients of cardiac transplantation have a threefold higher increase in the incidence of NMSC that occurs earlier after transplantation (mean: 2 years) as compared to recipients of renal transplants, most likely because of a more profound immunosuppression [26,31].

In contrast, gender of the recipient, type of donor (cadaveric or live), and duration of dialysis do not appear to affect the incidence of post-transplantation skin cancer [12,32,33].

5. Organ transplant recipients are at increased risk for developing malignant melanoma

Epidemiologic studies demonstrate that OTRs are at a 2–8-fold increased incidence of de novo melanoma after transplantation [34]. It has to be noted that a surprisingly high proportion of post-transplant melanomas arise in dysplastic nevi. This observation indicates that immunosuppression in a host with a melanoma precursor confers a particular susceptibility to neoplastic transformation. Interestingly, the sudden appearance of both benign and neoplastic nevi in transplant recipients has been reported [21]. Obviously, OTRs with de novo primary cutaneous malignant melanomas are unable to react with an appropriate cellular immune response to these neoplastic melanocytes, permitting rapid evolution of the malignant tumor and metastatic spread. In addition to the de novo development of malignant melanoma after transplantation, one has to be aware of the concern of donor-derived melanoma, which frequently has been shown to affect the transplant, metastasizes rapidly in OTRs, and in many cases results in the death of the recipient within months [21].

6. Other types of skin cancer including Kaposi's sarcoma and Merkel cell carcinoma have an increased incidence and prevalence in solid organ transplant recipients

Immunosuppression and other factors lead in OTRs to an increased incidence of other types of cutaneous malignancies besides SCC, BCC and malignant melanoma. Kaposi's sarcoma (KS) has been reported to have an appr. 84-fold increased incidence in solid OTRs as compared to the general population [9] and Merkel cell carcinoma also appears to be more common in OTRs [35,36]. Other tumors,

including atypical fibroxanthoma, dermatofibrosarcoma protuberans, angiosarcoma, verrucous carcinoma, leiomyosarcoma, and cutaneous T cell lymphoma, are suspected to also have an increased incidence and more aggressive growth behaviour in OTRs. However, it has to be noted that this expert opinion still needs to be confirmed. For no large-scale studies have been performed the actual incidence of these rare cutaneous malignancies in OTRs is unknown and available data are based solely on case reports [37,38].

7. Immunosuppressive treatment: both beneficial and adverse effects

After solid organ transplantation, patients in general need a lifelong immunosuppressive medication which plays an important role in the cancerogenesis of NMSC and various other malignancies. It is well documented in the literature that the intensity and duration of immunosuppression is positively correlated with the development of cancer [8,25]. However, it has to be noted that the relative risk of individual immunosuppressive therapy regimens for cancerogenesis of NMSC is still unclear.

At present, four different classes of immunosuppressive medications can be distinguished according to their different sites of cellular and molecular action: inhibitors of cell proliferation, amplification signals, STATs (signal transducers and activators of transcription) or DNA synthesis [39]. Due to their relatively early introduction into clinical medicine, most retrospective data exist for azathioprine and cyclosporine. Azathioprine is an anti-metabolite that inhibits the de novo synthesis of purins. Cyclosporine belongs to the group of calcineurin inhibitors that modulate the amplification of intracellular signals. More recently, biologics and other very effective immunosuppressive drugs were introduced into clinical practice such as muromonab-CD_3 (orthoclonal OKT_3), basiliximab, daclizumab, mycophenolate mofetil (MMF), tacrolimus, everolimus and sirolimus [40,41]. In general, the causality between a single immunosuppressive medication and the development of cancer is difficult to analyze because usually a combination of different immunosuppressive drugs is used and changes in individual immunosuppressive therapy regimens including changes in dose rates are common practice in transplantation medicine.

The association of individual immunosuppressive therapy modalities and cancer incidence has been analyzed. Jensen et al. reported in 1999 that kidney transplant recipients receiving cyclosporine, azathioprine and prednisolone had a 2.8 times increased risk of developing cutaneous SCC as compared to kidney transplant recipients that received only azathioprine and prednisolone [9]. Dantal et al. demonstrated in a randomized comparison of two cyclosporine regiments in kidney graft recipients that the dose of cyclosporine significantly modulates the risk for the development of cancer [42]. In this study, the low dose regiment was associated with a reduced incidence of malignancies as compared to the high dose regiment [42].

Results of the studies analyzing the association of cancer risk with immunosuppressive therapies are still a matter of discussion. Penn et al. reported 1999 that skin cancers occurred more frequently in recipients receiving azathioprine (40.6%) and azathioprine combined with cyclosporine (34.2%) compared with those treated with a monotherapy of cyclosporine (25.1%) [43], although he depicted that cyclosporin A accelerates the development of de novo malignancies (after 26 months) in comparison to azathioprine and prednisolone (after 64 months) [43]. Similar results were reported by Thiel et al. in a comparison of kidney transplant recipients receiving cyclosporine versus a treatment with azathioprine and prednisolone [44].

Immunosuppressive agents are also accused to influence the growth behaviour, including the agility and invasiveness of neoplastic cells in a direct cellular way. In agreement with this, Hojo et al. reported in 1999 a direct cyclosporine A-induced TGF-beta dependent tumor progression in SCID mice [45]. Interestingly, Stallone showed in 2005 that sirolimus blocks the progression of dermal Kaposi's sarcoma in kidney transplant recipients resulting in a complete tumor regression within 3 months [46].

Only a few studies analyzed the potentially carcinogenic side-effects of immunosuppressive therapy modalities. Krupp et al. investigated the side-effect profile of cyclosporin A in patients with severe psoriasis: skin cancer occurred in 0.7% and the SCC/BCC ratio was 6:1 which was suggested to be at least in part be caused by previous treatment with PUVA and/or methotrexate [47].

8. Vitamin D deficiency in solid organ transplant recipients: an underrecognized risk factor for a broad variety of severe diseases

It is generally accepted that, due to immunosuppression, OTRs are at increased risk for UV-induced NMSC. As a result, OTRs are advised to protect themselves from exposure to solar or artificial UV-radiation. However, this represents a serious dilemma, for appr. 90% of the human body's requirements in vitamin D have to be photosynthesized in the skin from 7-dehydrocholesterol by the action of UV-B-radiation (Fig. 1). Since sunlight (UV-B) is the major source of vitamin D for most humans, OTRs, who avoid the sun or wear sun protection, therefore are at risk of developing vitamin D deficiency. Vitamin D deficiency is not only associated with increased risk for bone diseases, but is associated with other severe health problems including various types of internal malignancies (e.g. colon, prostate- and breast cancer) [48–50]. Considering these negative effects of UV-protection, screening for vitamin D deficiency in OTRs is warranted. Serum levels of 1,25-dihydroxyvitamin D_3 [1,25(OH)2D, calcitriol] have been monitored in renal transplant patients since it was realized that the kidneys were responsible for the conversion of 25-hydroxyvitamin D_3 [25(OH)D] to $1,25(OH)_2D$. Patients with bone disease after kidney transplantation are often monitored for their serum $1,25(OH)_2D$ levels. $1,25(OH)_2D$ and its active analogs such as alfacalcidiol and paracalcitol have been shown to be effective in prevention of post-transplantation bone loss [51–53]. However, serum levels of 1,25-dihydroxyvitamin D_3 in the normal range do not protect against the broad variety of independent diseases that are associated with deficient or insufficient 25(OH)D serum levels [54,55]. We have recently analyzed the serum levels of 25(OH)D, which is the major circulating form of vitamin D and is used to determine the vitamin D status of patients in OTRs [54,55]. These patients need to protect themselves for medical reasons from solar and artificial UV-exposure and therefore are at risk to develop vitamin D deficiency. Serum 25(OH)D levels were analyzed in renal transplant patients with adequate renal function and in an age- and gender-matched control group at the end of wintertime [55]. All renal transplant recipients had practised solar UV-protection post-transplantation. Serum 25(OH)D levels were significantly lower in renal transplant recipients as compared to controls ($p = 0.007$) [55]. Geometric mean (with 95% confidence interval) in renal transplant recipients was 10.9 ng/ml (8.2–14.3) compared to 20.0 ng/ml (15.7–25.5) in the control group [55]. In 10 of the 31 renal transplant recipients serum 25(OH)D levels were undetectable (<4 ng/ml). Five other patients had 25(OH)D levels < 15 ng/ml. In renal transplant recipients, serum creatinine levels were $\leqslant 4$ mg/dl post-transplantation [mean: 1.7 mg/dl, normal range: 0.7–1.2 mg/dl (male), 0.5–0.9 mg/dl (female)]; parathyroid hormone ranging from 37 to 1058 pg/ml [mean: 198.7 pg/ml, normal range: 15–55 pg/ml] [55]. To investigate whether vitamin D deficiency is characteristic for OTRs or can be found in other sun-

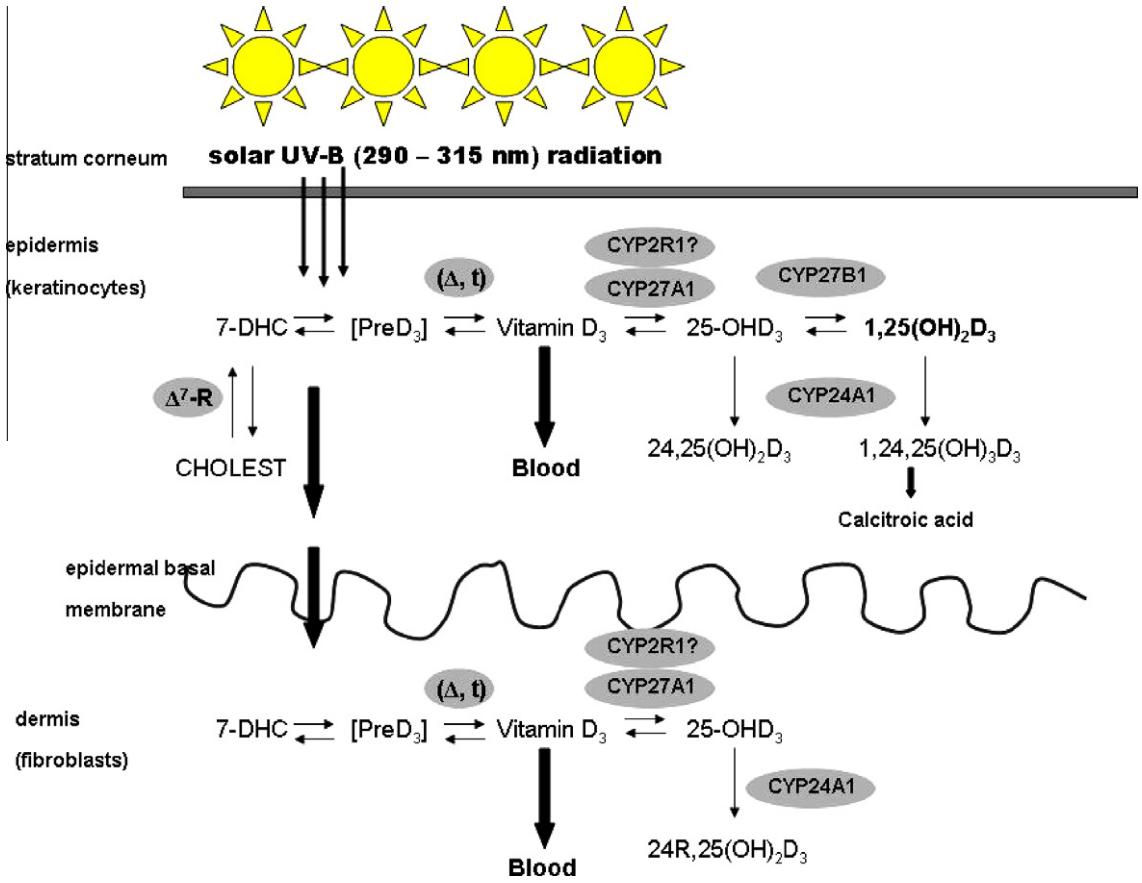

Fig. 1. An illustration of the cutaneous vitamin D endocrine system in human skin. The skin represents an unique tissue in the human body's vitamin D endocrine system, producing various vitamin D metabolites for endocrine, paracrine and autocrine signalling. Notably, vitamin D is photosynthesized in the skin (epidermis and dermis) by solar or artificial UV-B-radiation, before it is transferred to the blood for endocrine signalling to cover the body's needs in vitamin D. Biologically active 1,25-dihydroxyvitamin D_3 is synthesized in many skin cells, where it acts locally (most skin cells express VDR) and regulates a broad variety of independent cellular functions via autocrine/paracrine pathways.

light-deprived risk groups as well, we have analyzed basal 25(OH)D_3 serum levels in a small group of patients with Xeroderma Pigmentosum (XP, $n = 3$) and basal cell nevus syndrome (BCNS, $n = 1$) at the end of winter (February/March) [56]. 25(OH)D_3 levels in all four patients were markedly reduced with a mean value of 9.5 ng/ml (normal range: 15.0–90.0 ng/ml) [56]. In conclusion, we demonstrated decreased serum 25(OH)D_3 levels in OTRs and other sunlight-deprived risk groups [54,56]. Recently, the high prevalence of vitamin D deficiency in OTRs has been confirmed by other investigators [57,58].

10. A paradigm shift in the diagnosis, treatment and general management of skin malignancies in solid organ transplant recipients

10.1. General principles

It has now become evident that the most important element of preventive management of skin cancer in transplant recipients is patient education and rigorous solar and artificial UV-protection [59]. Previously, patients were referred to dermatology or to dermatologic surgery only after having developed significant skin neoplasms. In recent years however, a paradigm shift occurred and multidisciplinary approaches to patient care have been increasingly implemented with the integration of multiple services, including dermatology, dermatologic surgery and Mohs' micrographic surgery, transplant surgery, nephrology, cardiology, and hepatology. At present, the clinical paradigm is one of preventive education, early intervention, and administration of prophylactic regiments against skin malignancies.

To realize this paradigm shift and to implement such an intervention, dermatology clinics are increasingly established onsite in academic centers, within the transplant unit. The existence of a dermatology clinic within the transplant center greatly facilitates patient education regarding protection against artificial and solar UV-radiation, prevention of skin cancer in general and surveillance in the time period after transplantation. Guidelines of care for OTRs include education in sun protection and self-examination; risk assessment based on skin type, history of skin cancer, standard follow-up intervals, and prophylaxis for high-risk groups. Additionally, patients are evaluated and assessed on risk of skin cancer development after receiving an organ transplant. Skin cancers have to be treated consequently according to their aggressive growth behaviour, emphasizing rapid and direct access to dermatology.

The implementation of a specialty dermatology clinic within the transplant center also allows the appropriate supervision of aggressively growing SCC and enable the investigation of the role of sentinel lymph node biopsies and new immunosuppressive regiments in the management of NMSC. Additionally, the implementation of a specialty dermatology clinic within the transplant center also strengthens communication with transplant surgery on the development of a strategic approach toward reduction of immunosuppression in high-risk patients.

All OTRs should be evaluated for skin cancer and educated on prevention as soon as possible after transplant. Very low-risk pa-

tients can be followed by their transplant physician on a regular basis and referred to the dermatology clinic in longer time intervals or if concern over any skin lesions arises. Any OTR who has multiple risk factors for the development of skin cancer after transplantation should be seen by a dermatologist either before transplantation or as soon as possible after receiving a transplant. In addition, they should be followed regularly by the dermatologist for a full-body skin examination. On the first visit with the dermatologist, OTRs should be educated on recognizing premalignant and cancerous skin lesions and encouraged to seek medical attention early if suspicious skin lesions develop. Patients should also be advised to perform skin self-examination on a regular (monthly) basis.

As outlined above, it is important to advise patients before transplantation, and to provide regular dermatological follow-up. In this context, we would like to strengthen the fact, that OTRs are at high risk to develop vitamin D deficiency, which is of high importance to detect and to treat [55–58,60]. Recommendations for the oral treatment of vitamin D deficiency have been reported previously [61–63]. A single dose of 50,000 IU vitamin D once a week for 8 weeks is efficient and safe. Another means of guaranteeing vitamin D sufficiency, is to give 50,000 IU of vitamin D once a month. Most experts agree that a daily oral dose of 1000–2000 IU vitamin D is effective in preventing vitamin D deficiency in risk groups. We would like to accentuate the fact that careful monitoring of vitamin D status and oral substitution in case of vitamin D deficiency is of high importance for OTRs. This will protect these patients sufficiently against the serious health problems of 25(OH)D deficiency without further increasing their risk to develop squamous cell carcinoma of the skin or other types of UV-induced skin cancer.

11. Sun protection and the importance to detect and to treat vitamin D deficiency

All OTRs should be continually advised to use appropriate sun protection because of their increased risk of developing skin cancer. OTRs should be advised to avoid solar and artificial UV-exposure whenever possible. Use of sunscreens containing titanium dioxide should be recommended to provide a physical block from solar UV-radiation. The sunscreen should be rated with a sun protection factor (SPF) of 30 or greater. Sunscreen should be applied every day to all solar UV-radiation-exposed skin areas, and it is helpful to encourage OTRs to keep multiple bottles of sunscreen in the car or elsewhere to guarantee continuous protection. It should be recommended that sunscreen should be applied every day, not just when solar UV-radiation exposure is expected. Protective clothing is also an important means of skin cancer prevention. OTRs should be advised to wear a wide-brimmed hat with a 4-inch brim on all sides when they are out in the sun. Wearing tightly woven long-sleeve shirts and long pants of darker color is also protective and should be recommended. Use of appropriate solar UV-radiation protection should be recommended at every follow-up visit with the dermatologist. However, we would like to accentuate the fact that, due to the lack of solar UV-exposure, careful monitoring of vitamin D status and oral substitution in case of vitamin D deficiency is of high importance for OTRs, to protect these patients sufficiently against the serious health problems of 25(OH)D deficiency.

12. Management of skin lesions

12.1. Actinic keratosis (AK)

AK have the same clinical appearance in OTRs as in the general population; however, they may be more numerous in the former. They typically appear on chronically solar UV-radiation exposed sites such at the face, scalp, extensor forearms, and dorsum of the hands. The lesions may appear as single or multiple discrete dry, rough, scaly plaques. Palpation may be helpful in the diagnosis of this type of lesion. Aks may progress to hypertrophic AKs or cutaneous horns characterized by a macular or papular base with a white, black, or yellowish keratotic cap. AKs are now considered SCC in situ that may progress to invasive SCC if left untreated. Histologically, AKs in OTRs have been found statistically more likely to demonstrate bacterial colonization, confluent parakeratosis, hyperkeratosis, increased mitotic activity, and verrucous changes [64]. Because of the increased risk of developing invasive SCC in OTRs, AKs should be managed consequently and treated aggressively. Follow-up visits for OTRs with AKs should be scheduled at least every 6 months [18]. Treatment regiments include cryotherapy, topical 5-fluorouracil (5-FU), electrodessication with curettage, topical treatment with imiquimod or photodynamic therapy (PDT). Any lesion that persists after appropriate therapy should be biopsied or excised to rule out progression to invasive SCC. Patients with multiple AKs may also be treated with topical medication, e.g. imiquimod, which has been approved for the treatment of AKs. It has to be noted that to date, there is no evidence that topical treatment with imiquimod confers risk to the transplanted organ.

The efficacy of topical PDT was compared with 5-FU in clearing epidermal dysplasia in OTRs, showing a greater efficacy of PDT in achieving complete resolution of lesions, its superior cosmetic outcome and patient preference over 5-FU, despite the initially higher levels of pain associated with PDT treatment [65].

While a number of studies demonstrated successful treatment of epidermal dysplasia in immunocompetent patients using topical PDT (with clearance rates ranging from 69% to 100%) [66–74], previous studies had clearly indicated reduced clearance rates in OTRs. Dragieva et al. [75] treated epidermal dysplasia (AK, CIS) in 20 OTRs and 20 controls with topical PDT using 5-ALA, and in a second study compared MAL PDT with placebo in the treatment of 129 AKs in 17 OTRs [76]. In the first study, the overall CRR in OTRs at 4, 12 and 48 weeks was 86%, 68% and 48% respectively, whilst in the second study, the overall CRR at 4 months was 90% (56 of 62) for PDT and 0 (0 of 67) for placebo. Schleier et al. [77] treated a total of 32 cutaneous lesions, comprising AKs, BCCs, keratoacanthomas and SCCs, in five OTRs and reported a CRR of 75% at 3 months. It has been discussed that the apparent decline in efficacy with time following PDT [75] may be due to either recurrence of inadequately treated lesions, or the appearance of new lesions at the treated site. Notably, de Graaf et al. [78] reported a randomized controlled trial in 40 OTRs where PDT showed no statistically significant effect on reduction of keratotic skin lesions on the arm treated with either one or two cycles of PDT. More recently however, Perrett et al. reported that topical MAL PDT was more effective than topical 5-FU in the treatment of epidermal dysplasia in OTRs [65]. The clearance rate of 89% at 6 months for topical PDT in that study was comparable to that reported in most existing open studies in both immunocompetent [66–74] and OTRs [75–77]. A number of possible explanations may account for why the efficacy of PDT was lower in the study of de Graaf et al in OTRs [78], as compared to the study of Perrett et al. [65], including: (a) the treated keratotic lesions in the study by de Graaf and colleagues were not histologically confirmed and were not all necessarily areas of epidermal dysplasia; (b) violet light (400–450 nm) was used in the study of de Graaf et al. [78], which has reduced penetration compared with the red light (600–700 nm) used by Perrett et al. [65]; (c) failure to remove lesional hyperkeratotic scale and crust before treatment may have prevented adequate penetration of photosensitizer in the study of de Graaf et al. [78]; (d) 5-ALA was used by de Graaf et al. which penetrates less deeply than MAL that was used by Perrett et al. [65]; (e) the treatment protocol of the study of de Graaf et al. [78] may not have been optimal with only half of the lesions treated twice but with a 6-months

gap in between rather than 1 week; and (f) the study sample of Perrett et al. [65] was small. Interestingly, Perrett et al. [65] did not experience a decline in CRR with time for PDT-treated lesions as reported by Dragieva et al. [75] and, once again, different methods may have partly accounted for this. It has been emphasized that such practical considerations may be of particular relevance in optimizing PDT for immunosuppressed individuals [79]. In the study of Perrett et al. [65], the improved outcome for PDT vs. 5-FU appears, at least in part, to reflect a poorer than expected clearance of epidermal dysplasia with 5-FU in the patient group. From data in immunocompetent patients, a 90% clearance rate should have been expected, as compared with the 11% CRR that we observed at 6 months. It was concluded that 5-FU regimens recommended for treatment of immunocompetent patients may not be appropriate for OTRs [65].

12.2. Squamous cell carcinoma (SCC)

An important step for the management of SCC in OTRs was the publication of guidelines by the International Transplant-Skin Cancer Collaborative (ITSCC). Based on this report, patients should be divided into low-risk and high-risk categories based on aggressive growth characteristics of the SCC.

12.3. Low-risk SCC

First, any lesion suspicious for SCC should be biopsied or excised. Electrodessication and curettage (ED&C) may be performed at the time of biopsy for those lesions that are clinically determined to be less aggressive [1,18,65]. For lesions judged to be low risk based on histology as well, treatment options include: cryosurgery with curettage, ED&C, surgical excision, or Mohs' micrographic surgery [1,18,65]. For those areas where conservation of tissue is a priority or for sites that are in anatomic areas of moderate risk, Mohs' micrographic surgery is the best option [1,18,65].

12.4. Aggressive SCC

For skin lesions that are determined to be aggressively growing based on clinical characteristics or histologic features, destructive techniques are not recommended. Aggressively growing SCC should be treated with excisional techniques, particularly Mohs' micrographic surgery. Other recommended options for complete excision include surgery with intraoperative frozen section evaluation, or excision with postoperative margin assessment. Margins should include the subcutaneous fat and 6–10 mm beyond any surrounding erythema [80]. If there is evidence of perineural involvement, invasion of surrounding bones or glands, unclear margins, or if the lesion persists after excision, then further evaluation is necessary. Radiation therapy should be considered in cases where there is perineural involvement or where there is inability to achieve clear margins [1,18,65]. Sentinel lymph node biopsy (SLNB) has been shown in small studies to be effective in identifying nodal disease in patients with SCC of the lip [1,18,65,81]. This option should be considered for patients with high risk SCC. The decision to decrease immunosuppressive therapy should be discussed with the patient's transplant team.

12.5. Metastatic SCC

Any patient with metastatic nodal spread should be evaluated for excision with therapeutic lymphadenectomy or primary radiation therapy (XRT). Patients with in-transit cutaneous metastasis who do not have lymph nodes that are positive for metastatic spread should have excision of the primary and satellite lesions. In these patients, Mohs' surgery is recommended. Chemotherapy, the use of systemic retinoids, and the reduction of immunosuppressive medication are other additional options that should be considered in patients with nodal spread or satellite lesions [1,18,65].

12.6. Multiple nonmelanoma skin cancers (NMSC)

Application of prophylactic topical retinoids or episodic 5-FU may be used in patients who develop multiple AKs or NMSC. In OTRs who develop more than five NMSCs in 1 year, prophylactic administration of systemic retinoids should be considered. It has been reported that the administration of systemic acitretin (30 mg/day) leads to a reduction in the incidence of SCC [82]. However, chemoprophylaxis with retinoids is problematic in OTRs because of the need for long-term therapy. Well known side-effects include hyperlipidemia, which should be treated consequently in OTRs. Any patient receiving systemic retinoids should have liver function tests and lipids checked on a regular basis. A rebound effect after discontinuation of retinoids, resulting in an increase in the number of skin cancers, has been observed [18,65]. Dermatologists should discuss the possibility of a reduction of the immunosuppressive medication with the transplant team for patients with more than 5–10 NMSC per year [83]. Recently, it has been analyzed whether common known polymorphisms in the regulatory region of the cyclooxygenase-2 (COX-2) gene (PTGS2) can be associated with NMSC predisposition after organ transplantation and whether cancer risks are associated with specific COX-2 gene haplotypes containing these polymorphisms [84]. In that study, it was demonstrated that COX-2 common variants −765G → C and −1195A → G appear to be associated with risk of NMSC, although in different ways in the SCC and BCC subgroups, indicating that environmental and genetic risk factors may play different roles in the outcome leading to these two phenotypes [84]. Recently, a comprehensive literature review was carried out to discuss relevant genetic polymorphism for the development of NMSC in organ transplant recipients [85]. These include genetic polymorphisms in glutathione S-transferase, interleukin-10, retinoblastoma and p53 genes. Additionally, genetic polymorphisms in the folate pathway, melanocortin 1 receptor and vitamin D receptor were discussed. The authors concluded that no single factor is causative in cutaneous carcinogenesis in transplant recipients and that most likely interactions of some of the above mechanisms with known environmental factors lead to increased risk [85].

12.7. Keratoacanthoma

Keratoacanthomas (KA) also have a similar clinical appearance in solid organ transplant recipients as in the general population. Clinically, they appear as dome-shaped nodules or papules with a central keratotic plug. They occur on solar UV-radiation exposed areas and can grow very rapidly. OTRs may have multiple KAs on solar UV-radiation exposed areas. KAs may not always be clinically distinguished from SCC and therefore should be treated with surgical excision. For OTRs with multiple KAs, systemic retinoids may be used.

12.8. Basal cell carcinoma (BCC)

BCC has the same clinical appearance in OTRs as in normal hosts. It presents as a pearly teleangiectatic papule or as a crusted, atrophic or ulcerated lesion. In contrast to the general population, OTRs have much higher incidence rates of SCC compared to BCC. BCC can be treated with various therapeutic modalities, including ED&C, surgical excision, or Mohs' surgery depending on the size of the lesion, its location and whether it is recurrent. Topical imiq-

uimod has also been approved for the treatment of superficial BCC in non-immunocompromised patients. Use of topical imiquimod in OTRs for superficial BCC has only been reported in a limited number of cases, but preliminary results are encouraging.

12.9. Malignant melanoma (MM)

MM has the same clinical appearance in transplant recipients as in normal hosts, but has a slightly higher incidence in transplant recipients. It has been recommended that surveillance for MM should be more aggressive in OTRs. Many centers have utilized full-body photography and dermatoscopy to follow patients with multiple pigmented nevi. Any lesion that is suspicious for MM should be biopsied or excised. Localized lesions should be treated with wide local surgical excision. In OTRs with MM that are more than 1 mm thick or that are ulcerated, sentinel lymph node biopsy may be useful. For kidney or pancreas allograft patients with metastatic MM, discontinuation of immunosuppressive medication should be considered [83].

12.10. Follow-up

OTRs with a history of one NMSC should be seen every 6 months by a dermatologist. OTRs with a history of multiple NMSC, high risk NMSC or MM, should be seen at least every 3 months. Sites of any previous cutaneous malignancy should be reevaluated at every examination. Regional lymph node exam should also be performed. If there is any suspicion of metastatic disease, further evaluation that may include laboratory or radiologic studies has to be performed [1,18,65].

13. The relationship between vitamin D status and the incidence of skin cancers

The relationship between vitamin D status and the incidence of skin cancers has been investigated previously [86–90]. While earlier studies that were focused on measuring the biologically active metabolite 1,25-dihydroxyvitamin D_3 in the serum did not support the hypothesis that vitamin D deficiency may be a risk factor for skin cancer incidence, newer studies analyzing 25(OH)D serum levels supported this hypothesis. Moreover, it has been reported that several VDR polymorphisms, that are associated with reduced transcriptional activity, may represent a risk factor both for increased incidence and poorer prognosis in melanoma and nonmelanoma skin cancer [91,92].

14. Summary and conclusions

The introduction of organ transplantation in clinical medicine has resulted in a constantly increasing, large population of patients that are chronically on immunosuppressive medication. It is well known that skin cancer, especially SCC, in this population has higher incidence rates, behaves more aggressively and has higher rates of metastasis. OTRs who have been treated for many years with immunosuppressive medication are at the highest risk for developing malignant skin tumors. Therefore, the intensity of surveillance for cutaneous lesions is of high importance in OTRs. A full-body skin exam at least once a year and more frequently if skin cancer or precancerous cutaneous lesions develop is recommended. Clinicians should not hesitate to biopsy or to surgically excise any suspicious skin lesion. Of high importance is also the education of OTRs about their increased risk. Protection against solar and artificial UV-radiation and monthly self-examinations are good ways to prevent and to recognize any new suspicious skin lesions. Patients are advised to always wear solar UV-radiation protection (e.g. clothing, sunscreen) before going outdoors. However, investigations have revealed that solar UV-B-exposure and serum 25(OH)D levels positively correlate with decreased risk for various internal malignancies (e.g. breast, colon, prostate, and ovarian cancer) and other severe diseases. As we have shown previously, renal transplant recipients are at high risk of vitamin D deficiency. A sunscreen with a sun protection factor (SPF)-8 reduces the skin's production of vitamin D by 95%. Clothing completely blocks all solar UV-B-radiation and this prevents any vitamin D production. Therefore, it is important to detect and treat vitamin D deficiency in solid organ transplant recipients. Optimal management of these patients requires communication between the transplant teams and the treating dermatologist and other clinicians. For advanced or metastatic disease, collaboration between clinicians of different disciplines, including the transplant team, dermatologists and radiation oncologists is also essential. In the future, dermatology clinics that are integrated into transplant centers may make it easier to manage and to treat OTRs, may make an interdisciplinary approach more effective and may thereby improve the clinical outcome in OTRs.

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