Azathioprine, UV light, and skin cancer in organ transplant patients—do we have an answer?*

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The remarkable story of transplant medicine currently benefits more than 35,000 patients in the EU and US annually [1]. Patient and organ survival time has steadily increased over the years, and according to a recent analysis of 94,934 kidney transplant recipients, the half-life for kidney transplants has nearly doubled from 1988 to 1996 [2].

However, with increasing graft and patient survival, the focus of medical disciplines involved in the aftercare of transplant recipients is shifting towards managing the direct and indirect consequences of chronic immunosuppression [3,4]. The development of cutaneous infections and skin cancers is frequently observed in patients with impaired immunosurveillance, culminating in significant morbidity and even mortality in organ transplant recipients (OTR) [5].

A comprehensive study examining the US-Medicare billing claims of more than 35,765 kidney transplanted patients showed a 7.43% cumulative incidence of non-melanoma skin-cancer only 3 years post-transplantation [6]. In contrast to the general population, squamous cell carcinoma (SCC) is the predominant malignancy in OTR [7]. Chronic sun exposure, pre- and post-transplantation, appears to be the primary pathogenic agent, and is frequently cited as a major risk factor for SCC.

The vast majority of skin cancers, especially SCC, occur in the sun-exposed areas of the skin. Ultraviolet radiation consists mainly of UVA (320–400 nm) and UVB (290–320 nm) radiation, while UVC (270–290 nm wavelength) is generally filtered by the ozone layer in the stratosphere. Shorter wavelengths (UVB) are directly mutagenic through the formation of DNA photoproducts such as pyrimidine dimers. Longer wavelengths, (UVA), on the other hand, induce the production of reactive oxygen species (ROS) with indirect mutagenic effects. The associated photooxidative stress results in the formation of DNA mutations including C-T transitions and transversions, as well as the induction of matrix metalloproteinases and p53 mutations [8]. UVA, the major component of solar radiation, has gained special attention in modern sun screen development, because of its ability to penetrate the skin down to its basal layers containing the stem cells [8]. Cumulative UV exposure, in particular pre-transplantation, can hasten the onset of SCC post-transplantation in patients transplanted after the age of 50 [9]. As the cumulative dose of immunosuppressive medication escalates, paralleling increasing survival years post-transplantation, a dramatic increase in the prevalence of NMSC is being observed in the ever-growing population of ‘transplant veterans’ worldwide [10].

Various studies in the past and present have dealt with possible mechanisms by which immunosuppressive drugs may accelerate the development of skin cancer in OTR. A direct association to carcinogenesis has been ascribed to ciclosporin [11], for example, but related mechanisms might be relevant to other medications as well. Chronic immunosuppression is also responsible for the impairment of systemic and local immune surveillance, and can provoke the compromised elimination of dysplastic keratinocytes [12]. Determining the individual impact of each immunosuppressive drug on the development of skin cancers in a clinical setting is further complicated by the administration of combination therapies, as well as by the presence of more than one medication in the system. Frequently observed alterations of immunosuppressive regimens due to non-dermatological complications have also been known to be conducive to skin cancer. [13] Clinical studies comparing different immunosuppressants in regard to their correlation with...
increased tumour incidence have generated conflicting results. Whereas some reports show a significant impact of ciclosporin on the incidence of skin cancer, others failed to confirm any differences when comparing the effects of azathioprine (Aza) or even tacrolimus (Tac) [14–17].

An article by O’Donovan et al. [18] recently published in Science magazine highlights the association of Aza with selective UVA photosensitivity. The thiopurine Aza acts as a prodrug of thioguanine nucleotides, causing an accumulation of 6-thioguanine (6-TG) in cellular DNA. Whereas normal DNA does not absorb significant amounts of UVA wavelengths (320–400 nm), 6-TG has an absorption peak at 342 nm. Consequently, the absorption of UVA results in the formation of ROS which have previously been linked to DNA-damage and the development of cutaneous malignancies. The increased susceptibility of 6-TG-treated cell-lines to UVA, demonstrated in this study, supports the premise that DNA 6-TG increases the biological effectiveness of UVA 2-fold. In a clinical setting, patients being treated with Aza, at a dose of 1–2 mg/kg body weight, experienced 0.02% 6-TG substitution of DNA guanine, whereas no 6-TG was detected in skin DNA of patients not taking Aza. This in-vitro data offers important clues to the evolution of the skin cancer plight in OTR. Furthermore, in patients treated with Aza, a significant reduction in the minimal erythemal dose (MED) for UVA and solar-simulating radiation was detected, indicating persistent DNA damage in human skin and an increased susceptibility to UVA [19]. This selective UVA sensitivity in connection with Aza treatment correlates with the formation of 6-TG DNA photoproducts.

The findings reported by O’Donovan and colleagues demonstrate the fact that normal exposure to sunlight may induce a cascade of reactions in the skin of patients taking Aza, ranging from the induction of oxidative stress and mutagenic DNA lesions, to the development of malignancy. For transplant recipients, especially in the case of long-time survivors, Aza is still part of the patient’s daily immunosuppressive regimen. The alarming incidence of skin cancers in these patients, in particular SCC, renders evident the need for therapeutic action. In spite of the lack of comprehensive data regarding the carcinogenic impact of Aza compared with mycophenolate mofetil (MMF), MMF is widely substituted for Aza in patients receiving de novo transplantation, or for those suspected of being at increased risk for development of skin cancer [20]. Our preliminary data on a 3-year prospective follow-up of a collective of 1500 kidney and heart transplant patients maintained on a triple therapy regimen of either CsA + Aza + Prednisolone(Pred), CsA + MMF + Pred, Tac + Aza + Pred or Tac + MMF + Pred showed a significantly lower cumulative incidence of SCC in the Tac + MMF + Pred group compared with Tac + Aza + Pred (P < 0.0079). Patients receiving CsA + MMF + Pred had a tendency towards lower SCC incidence over CsA + Aza + Pred, although the results were statistically insignificant (data presented at the 62nd Annual Meeting of the American Academy of Dermatology 2004 in Washington DC, USA). There is clear evidence of in-vitro, in-vivo and clinical antineoplastic properties in rapamycin (Rapa) [13]. Several studies indicate that Rapa inhibits the growth of many malignant cells in cell culture [21]. Others have shown that Rapa reduces phosphorylation of p53 after UVB exposure [22] and demonstrated Rapa-mediated inhibition of primary and metastatic tumour growth by angiogenesis in a mouse model [23]. A recent retrospective analysis comparing mTOR vs calcineurin-based immunosuppression in 33 000 patients with primary solitary kidney transplants revealed that patients treated with mTOR-based immunosuppression experienced a 59% lower relative risk of developing new cancers (relative risk 0.412, 95% CI 0.256, 0.663) than those given calcineurin-based therapy in a risk adjusted multivariate analysis (P = 0.0003) [24].

The question now is how to best apply the conclusions of these findings, in order to reduce the risk for post-transplant patients of incurring serious cutaneous consequences from long-term immunosuppressive treatment. Certainly Aza is not the only immunosuppressant that can be blamed for the development of cutaneous malignancies in organ transplant patients. However, the clinical and laboratory data presented by O’Donovan and others clearly support the need for further exploration of immunosuppressant drugs regarding their epidemiological and functional impact on post-transplant SCC. Considering any individual case of a patient, we would strongly suggest substituting those immunosuppressive drugs with clear evidence of a stronger association with skin cancer with those connected with a less stronger (MMF) or even negative (Sirolimus, Everolimus) skin cancer risk.

Furthermore, it is of utmost importance to emphasize to transplant patients the necessity for a consistent use of sun-screens with UVA as well as broad UVB protection. Post-transplant skin cancers are not exclusively an issue for the dermatologist. Being a major cause of morbidity in OTR, skin cancers represent an interdisciplinary challenge for every medical discipline involved in the aftercare of this patient group and only in close, mutual collaboration will we be able to adequately contend with it.

Conflict of interest statement. C. Ulrich has done talks for Novartis, Roche and Wyeth in the past.

References


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