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Organ transplantation and cutaneous squamous cell carcinoma: progress, pitfalls and priorities in immunosuppression-associated keratinocyte carcinoma

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The immune system plays a critical role in skin cancer development, dramatically illustrated by its increased risk in immunocompromised populations. Keratinocyte carcinoma (KC), in particular cutaneous squamous cell carcinoma (cSCC), are overwhelmingly the most common skin tumours in this context and are poised to rise steadily over the next decade. Four articles in this edition of the *BJD* draw upon evidence from research on cSCC in organ transplant recipients (OTRs). The authors are members of the Keratinocyte Carcinoma Consortium (KeraCon) Immunosuppression Working Group.

The articles provide an overview of the field, covering key areas of epidemiology (Madeleine *et al.*);[1] pathogenesis (Harwood *et al.*);[2] risk prediction models (Lowenstein *et al.*);[3] and current research priorities (Blomberg *et al.*).[4] Although advances have been made, there remain important evidence gaps that are limiting development of more effective treatment and prevention strategies for cSCC in OTRs. Progress in this field is of direct relevance to the growing challenges of KC in other immunocompromised populations, including those with autoimmune and inflammatory disorders treated with immunosuppression, HIV/AIDs and haematological malignancies. Perhaps most importantly, the model of accelerated cSCC development and progression that these high-risk patients represent has the potential to provide needed insights into age-related squamous carcinogenesis and its treatment and prevention in the general population.

Nearly 120 000 organs are transplanted worldwide each year (http://www.transplant-observatory.org) and survival continues to increase. The benefits are enormous but, as summarized by Madeleine *et al.*,[1] the overall risk for any cancer is increased approximately two- to sixfold compared with the general population. cSCC risk is elevated at least 100-fold in light-skinned populations, a burden complicated further by tumour multiplicity and a potentially aggressive clinical course. Although this risk is indisputable, poor registration of cSCC means that absolute incidence and mortality are not well defined. To remedy this deficit, we need to support prospective epidemiological studies to achieve a more definitive

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Conflicts of interest

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understanding of the excess risk of KC. Such studies are methodologically challenging but will be crucial in informing the design of screening and surveillance protocols and in ensuring that such protocols are appropriately stratified and targeted. Consortia such as KeraCon, SCOPE (Skin Care in Organ Transplant Patients, Europe), the ITSCC (International Transplant Skin Cancer Collaborative) and the BSSCII (British Society for Skin Care in Immunocompromised Individuals) aim to facilitate sharing data across research groups to achieve this goal.

Research efforts investigating the pathogenesis of OTR cSCC, reviewed by Harwood *et al.*,[2] point to a complex interplay between the main environmental carcinogen, ultraviolet radiation and dysregulated immunosurveillance, together with additional cofactors including direct procarcinogenic effects of immunosuppressive and other drugs, oncogenic viruses (in particular beta-genus human papillomaviruses) and host genetic susceptibility factors. Tumour-specific genetic and epigenetic changes appear to be similar to those in cSCC in immunocompetent patients, and alterations in the tumour microenvironment are generally more ‘permissive’ to cancer progression, although published data are few.

Unravelling the interdependencies of these diverse and often synergistic cofactors is a daunting task, yet it may hold the key to explaining observed differences in the epidemiology, clinical features and biological behaviour of cSCC in both OTRs and other populations. Defining the relative contributions of these cofactors and molecular changes will be important in guiding future opportunities for developing predictive and prognostic biomarkers, as well as more targeted therapeutic and preventative interventions.

Progress has been made in recent years in OTR cSCC treatment, prevention, screening and surveillance, but there remain significant uncertainties. Blomberg *et al.*[4] summarize current knowledge in this area and highlight those research gaps of particular significance in better informing delivery of skin cancer care to OTRs. The evidence informing treatment for primary cSCC in OTRs is even more limited than that for the general population, in whom there are few prospective, randomized controlled trials and limited nonrandomized studies to guide decision making.[5] Evidence-based data guiding management of regionally advanced or metastatic cSCC are scarce – an area of seriously unmet clinical need in current skin cancer practice – and as the great majority of clinical trials specifically exclude OTRs, this may prove to be a significant obstacle to progress.

Secondary prevention of cSCC is a priority given that 75% of OTRs have a further KC within 5 years of the first.[1] Modification of maintenance immunosuppression is an obvious starting point, yet information about how exactly drug regimens are most effectively revised is incomplete. The most convincing data exist for conversion of maintenance immunosuppression to mammalian target of rapamycin inhibitors such as sirolimus, but considerable uncertainties remain and the exact risk–benefit threshold to guide this strategy has not been adequately defined.[6] Systemic retinoids have been used for many years in chemoprevention of cSCC in OTRs, but they are not licensed for this use and no formal prescribing guidelines exist. Capecitabine, an oral prodrug of 5-fluorouracil, also appears clinically effective in retrospective studies, but no RCTs have been undertaken.

A recent development has been the possibility of chemoprevention with oral nicotinamide:[7] in a phase III trial from Australia, it significantly reduced actinic keratosis (AK) and KC in high-risk immunocompetent patients and has more recently shown some efficacy in OTRs. Larger trials are now required to confirm this finding. The relative efficacy, indications for, and sequencing of these diverse secondary prevention approaches need urgent clarification, but designing high-quality, randomized trials to address these questions is complex.[8]

Primary prevention efforts are gaining momentum and ideally would start in the pretransplant period wherever possible. Current consensus guidelines promote strict adherence to photoprotection measures, but justification is limited. Although regular sunscreen use prevents cSCC in the general population, the extent that this is true with the additional driver of immunosuppression is unclear, and support for its efficacy is limited to a nonrandomized, prospective study from Germany, which has yet to be replicated in larger RCTs.[9] Given the relatively rapid development of AK and cSCC, OTRs are an attractive group in whom to investigate novel photoprotection approaches. For example, results from trials of T4 endonuclease and afamelanotide in OTRs are awaited.[4] By the same token, future clinical research in OTRs may provide a more rapid answer to the other important unresolved question of whether treatment of AK and field cancerization is effective in reducing cSCC risk.[8]

With growing numbers of OTRs worldwide, the development of cost-effective skin cancer screening and surveillance protocols that ensure optimal deployment of limited healthcare resources is a research priority. Ongoing research into the pathogenesis of cSCC in OTRs may yield clinically useful biomarkers to identify the patients at greatest risk and allow rationalization of surveillance, but present risk prediction is limited mainly to known clinical risk factors. Lowenstein *et al.*[3] summarize the risk prediction tools currently available to clinicians for estimating individual KC risk post-transplant. Three have been validated and incorporate domains such as patient demographics, pigmentation, ultraviolet exposure and pretransplant skin history, but all have significant limitations. A more accurate tool for optimizing screening and surveillance that is easily applicable in a routine clinical context is a priority. Only future research involving large and demographically inclusive OTR cohorts will achieve these goals.

In conclusion, the four reviews brought together in this issue of the *BJD* highlight both progress and research gaps in the epidemiology, pathogenesis, treatment and prevention of cSCC following solid organ transplantation. This high-risk patient group presents a compelling model of accelerated skin carcinogenesis and has provided important insights relevant to KC, not only in other immunocompromised patient populations, but also in the general population. Indeed, it is likely that future progress in improving patient outcomes for cSCC will greatly benefit from continuing research in transplant recipients.

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