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Published in:
Journal of the European Academy of Dermatology and Venereology

DOI:
10.1111/jdv.15843

Publication date:
2019

Document Version
Peer reviewed version

Treatment approaches in immunosuppressed patients with advanced cutaneous squamous cell carcinoma

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Conflict of interest

None.

Funding Source

None.

Abstract

Immunosuppression, both iatrogenic and disease-related, is associated with a greatly increased incidence of cutaneous SCC (cSCC) and with aggressive cSCC and worse disease outcomes. Consequently, rapid access to skin cancer services and prudent surgical choices, such as circumferential margin assessment, are essential when treating advanced cSCC in an immunosuppressed (IS) patient. For high-risk cancers and for control of cSCC multiplicity, additional strategies should be actively considered within the multidisciplinary clinical care team. These include minimisation or revision of immunosuppressive medications, systemic chemoprevention (including retinoids, nicotinamide, capecitabine) and adjuvant therapies

such as radiotherapy. Unfortunately, there is a relative paucity of good evidence for many of these treatments in the IS. Systemic treatments for metastatic cSCC are often contraindicated in organ transplant recipients, notably checkpoint inhibitor immunotherapy. There are also toxicity concerns with some conventional chemotherapies and EGFR inhibitors. Until recently, clinical trials have largely excluded immunosuppressed individuals. Development of more effective treatment for advanced cSCC in this high-risk group and prospective clinical trials are now research priorities.

Introduction

Immunosuppression (IS) is a strong risk factor for the development of cutaneous SCC (cSCC). cSCC are frequently multiple and disease-related outcomes are significantly worse in organ transplant recipients (OTR) and patients with haematological malignancies[1,2,3]. Loco-regional recurrence is more common[4] and a recent national UK study found that IS doubles the risk of metastatic cSCC[5]. This review will address the specific challenges of managing advanced cSCC in the context of immunosuppression, including specific surgical considerations, use of radiotherapy as primary and adjuvant treatment, and barriers to use of conventional chemotherapies, targeted agents and immunotherapies such as immune checkpoint inhibitors (ICI)[6,7]. Tertiary strategies to reduce risk involving alterations in immunosuppressive drugs and chemoprevention will also be outlined. Prospective clinical trials are now urgently needed to inform future improvements in treatment choices and standards of care.

Surgical Considerations in immunosuppressed patients with advanced cSCC

Complete surgical resection is central to primary disease control in immunosuppressed patients and Mohs surgery or complete circumferential peripheral and deep margin assessment is recommended. Certain immunosuppressed patient groups have a higher rate of subclinical margin extension, suggesting that Mohs surgery or other intraoperative margin assessment may be preferable[8,9,10], but this has yet to be tested in a prospective, randomised surgical trials.

Limited data exist on the risk of postoperative complications in immunosuppressed patients undergoing surgery. Some but not all studies report increased rates of post-operative wound infection compared to immunocompetent subjects. This may be confounded by the propensity to put immunosuppressed patients on antibiotic prophylaxis[11]. Larger, prospective studies are needed to determine infection rates and the benefit of prophylaxis, if any.

While there is an increased risk of surgical dehiscence in patients on sirolimus[12], the morbidity associated with skin dehiscence is low enough that most dermatologic surgeons will not stop sirolimus for primary skin cancer excision. Invasive procedures such as lymphadenectomy may require transition from sirolimus onto another agent. This needs to be balanced against the benefits of switching a patient with cSCC from calcineurin inhibitors (CNI) to sirolimus, in order to reduce disease burden.

Thus, significant gaps exist in our understanding of surgical management of immunosuppressed patients with advanced cSCC. Future studies should focus on the benefits of intraoperative margin assessment in achieving complete clearance, risks of postoperative complications and the benefit of prophylactic intervention and postoperative adjuvant therapies such as radiotherapy.

Radiotherapy

Primary radiotherapy is not a first-line option in most OTR with cSCC. OTR tend to be younger and more likely to develop multiple tumours at specific anatomic sites, and previous radiotherapy to a particular site will usually preclude its subsequent use. Nonetheless, radiotherapy is an important strategy where surgery is not feasible or involved margins cannot be easily managed surgically. Death from cSCC usually results from uncontrolled loco-regional recurrence which is especially true for immunosuppressed individuals who are more likely to develop aggressive cSCC characterised by a high rate of loco-regional relapse[1]. Combined treatment with surgery and radiotherapy is considered best practice for patients with cSCC metastatic to lymph nodes[13]. There are no prospective randomised trials testing the benefit of adjuvant radiotherapy, but retrospective reviews consistently report improved disease-free and overall survival in those where surgery was

combined with adjuvant radiotherapy to the nodal basins. The worse outcomes in immunosuppressed patients mandate a lower threshold for combined surgery and adjuvant radiotherapy, although each case should be considered on balance of benefits (reduced loco-regional recurrence rate) versus potential carcinogenesis (uncertain risk).

Minimisation of immunosuppression, switch to mTOR inhibitors, systemic retinoids, capecitabine and nicotinamide

Non-surgical strategies to minimize the incidence of cSCC in high-risk OTR include revision of immunosuppressive medications and use of chemoprevention. In order to prevent graft rejection in OTR, immunosuppressive drug regimens primarily include anti-proliferative agents (e.g. mycophenolate mofetil [MMF]), CNI (e.g. tacrolimus, cyclosporine) and prednisone[14]. Reduction or revision of immunosuppressive drugs is generally advised in OTR with a history of aggressive or multiple cSCC[15]. In these high-risk OTR, IS should be maintained at the lowest level compatible with adequate graft function[16], limiting multi-drug regimens whenever possible[15].

IS also has varying degrees of direct carcinogenic potential. Azathioprine, for example, is associated with both an increased incidence and the potential to develop more aggressive cSCC in OTR[17]. Carcinogenic potential of MMF is significantly lower than azathioprine; hence transition from azathioprine to MMF is recommended for high-risk patients[16].

Another approach to reducing the risk of cSCC in high-risk patients is to transition from a CNI to an mTOR inhibitor (sirolimus or everolimus). CNI, through an increase in VEGF and TGF-B, can increase the rate of invasion and metastasis[16]. Although the full immunologic sequela of mTOR inhibition is not fully understood, these medications might have antineoplastic effects secondary to decreased tumour angiogenesis[16]. The rate of cSCC in patients treated with mTOR inhibitors is significantly reduced compared with calcineurin inhibitors. In one study of 120 kidney recipients with a history of at least one cSCC, patients treated with sirolimus were significantly less likely to develop cSCC compared to those treated with CNI (22% versus 39%, p=0.02)[18]. An additional study of 155 kidney recipients with a history of at least one cSCC demonstrated a 50% reduction in the rate of cSCC after one year[19]. Both studies had a high rate of drug discontinuation due to adverse effects[18,19],

but doses used in these early studies were arguably too high. Five-year results show a maintained benefit with mTOR inhibition provided the switch was conducted in early, not advanced, carcinogenesis[20].

Acitretin is the main chemoprophylactic retinoid for OTR at high-risk of SCC. Criteria for starting acitretin include multiple cSCCs [e.g. >2-5 per year]; a single cSCC with high metastatic risk; or a locally-recurrent or metastatic cSCC. Low-dose acitretin (0.2-0.4 mg/kg/day for a minimum of 12 months) reduced cSCC development in high-risk OTR in the first three years of treatment[21]. Regimens vary, but acitretin is often started at a low dose (e.g. 10 mg every other day) with the dose increased every 4 weeks according to side effects until a final dose (e.g. 20-25 mg daily) is reached[22]. Adverse effects which may limit use or result in discontinuation include muco-cutaneous changes such as cheilitis, hair loss and nail splitting. Fasting lipids and liver function tests should be checked monthly as the dose is increased, and every 3 months once stable and creatinine should be monitored in impaired renal function. Life-long treatment is necessary for maintenance of cSCC suppression and rebound cSCC development upon discontinuation is well recognised[22].

Capecitabine is another option in OTR with multiple cSCC. Capecitabine, a prodrug of 5-deoxy5-fluorouridine, is enzymatically converted to its active form, 5-fluorouracil in the liver[23,24]. Low dose capecitabine has been effective in reducing the incidence of cSCC in OTR in some case series: for example, capecitabine 0.5 to 1.5 g/m^2 was associated with a 68% reduction in cSCC per month over one year[24]. Side effects were diarrhoea, stomatitis, neutropenic fever, hand-foot syndrome, and gout[15,23]. Before treatment, screening for dihydropyrimidine dehydrogenase deficiency is required as capecitabine can cause severe toxicity in these patients[15].

More recently nicotinamide has shown benefit in reducing cSCC risk[25]. It both reduces UV radiation-induced immunosuppression and enhances DNA repair[25]. It has a favourable safety profile and is available over-the-counter[25]. In a phase III trial of immunocompetent individuals, nicotinamide 500mg twice daily reduced the development of cSCC by 30% at 1 year[25]. A phase II trial of 22 kidney recipients suggested a non-significant reduction in new cSCC[26]. An RCT is currently ongoing in Australia.

Conventional chemotherapy and targeted therapy

Data regarding the use of both conventional chemotherapy and targeted therapy with EGFR inhibitors in immunosuppressed individuals are limited. Specific considerations include dose adjustments with organ dysfunction, side effects and drug interactions[27]. For example, platinum compounds (e.g. cisplatin, carboplatin) cause myelosuppression and nephrotoxicity, and dose adjustments are required in renal impairment. Antimetabolite pyrimidine analogues (e.g. 5-fluorouracil, capecitabine) are myelosuppressive, associated with coronary artery vasospasm and dose adjustments are needed in liver impairment. Taxanes (e.g. paclitaxel) are myelosuppressive, require dose adjustments for liver impairment, and caution is required with comcomitant use of CYP3A4 inhibitors/inducers (e.g. antiretrovirals such as ritonavir, saquinavir, nelfinavir and efavirenz) and P-glycoprotein inhibitors (e.g. CNI, ritonavir and saquinavir). Data on use of anti-EGFR inhibitors (e.g. cetuximab) are limited. Although generally well-tolerated, neutropenia, infection, liver dysfunction and sudden cardiac arrest[27] have been observed. Fatal diffuse alveolar damage in two lung transplant recipients on cetuximab, necessitate the use of EGFR inhibitors with extreme caution in this group[28].

Immunotherapy

Use of checkpoint inhibitor immmunotherapy for immunosuppressed patients with advanced cSCC are restricted to case reports and case series[6]. Specific considerations include the potential risk of graft rejection; relevant immune-related adverse events on graft function, e.g. acute interstitial nephritis; possible reduced anti-tumour activity in the presence of immunosuppressive drugs and HIV; and effects on replication of HIV and hepatitis B/C viruses. Recent evidence - much of it from experience in advanced melanoma - suggests that the PD-1/PD-L1 axis is critical for maintaining organ tolerance whereas CTLA-4 blockade after induction of graft tolerance does not appear to affect allograft survival and this is reflected in rates of graft rejection which may be higher with anti PD-1/PD-L1 immunotherapy[6,7,29,30]. Although limited data in melanoma also suggest rates of response may be comparable in OTRs and immunocompetent individuals, the contribution to graft rejection of reduction of immunosuppression in this context has been raised[29]. Clinical trials are urgently required.

Retransplantation

Recent evidence suggests that the risk of cSCC increases with retransplantation, and these cSCC may be aggressive and associated with high mortality. In a multicentre retrospective study of 53 patients with previous post-transplant cSCC who received a second transplant, further cSCC developed in 74% of OTR after retransplantation. A higher proportion of these cSCC were histologically aggressive (26.4% versus 9.4% after the first transplant), and metastatic cSCC occurred in 10 patients of whom 5 died. Contributing to this risk were the older age and increased duration of IS, both known risk factors for aggressive SCC, and also use of azathioprine and T-cell depleting antibodies. Conversely, five patients in this series were retransplanted after an aggressive SCC, and this did not recur after the second transplantation suggesting that a history of aggressive SCC may not necessarily preclude retransplantation[31].

Conclusions

Advanced cSCC are more frequent and more challenging to treat in immunosuppressed patients. Furthermore, this is an area with very few robust data to guide decision-making. Consequently, consensus and sharing of best practice underpin current treatment strategies in this context. Alternatives to checkpoint inhibitors are required for OTR and this needs to become an area of active scientific and clinical endeavour. In the meantime, the mainstay of management must be prevention, including patient education, photoprotection, skin surveillance and aggressive treatment of pre-cancerous actinic keratoses and field cancerisation.

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