Skin cancer prevention in solid organ transplant recipients

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Organ transplantation in the 21-th century

- Organ transplantation is an alternative for patients with end-stage organ disease
- The number of performed transplantations worldwide increases constantly
- Major advances in treatment lead to prolonged transplant survival
- Long-living organ transplant recipients (OTRs) present variety of new and changing medical complications and treatment challenges
The changing face of OTRs morbidity over the years

- Acute rejection after transplantation was major problem after transplantation in the 60-s - early 70-s
- More aggressive immunosuppressive therapy was introduced for fighting rejection episodes
- Heavy immunosuppression led to severe infections and need for prophylactic treatment
- Lately, new therapeutic agents emerged, survival improved and morbidity profile changed
Organ transplantation and cancer

- Solid organ transplant recipients have an increased cancer incidence compared to the general population.
- The estimated overall cancer risk in OTRs is 2-3 times higher than in the immunocompetent population.
- In recent studies, there was elevated risk for 32 different malignancies, some related to known infectious agents.
- Skin cancer is the most common malignancy post transplantation.

Skin cancer in organ transplant recipients

- Non melanoma skin cancers (NMSCs) account for 95% of skin cancers in OTRs
- Relative risk increases steadily with time
- Incidence starts growing 2 – 5 years post transplant for NMSCs, rare tumors (melanoma, Merkel cell carcinoma) show later peaks
- Tumors appear some 10 – 15 years earlier in life compared to the general population

Unique characteristics of skin cancer in OTRs

- NMSCs have aggressive biological behavior
- SCC:BCC ratio is inverted (4:1)
- Higher rates of local recurrence after initial treatment present are characteristic
- Greater tendency toward distant metastases and in-transit metastasis phenomenon in SCC were described
- Some patients develop “catastrophic” number of tumors
- Morbidity and mortality are increased
Concepts on skin carcinogenesis

- Different factors are involved in skin cancer formation after transplantation
- Cumulative sun exposure, Fitzpatrick skin type and the ability to sunburn, all present major risk factors
- UV range and sun protective practices are found to have important influence
- Prominent impact is attributed to type, duration and intensity of immunosuppressive treatment

Skin cancer education

- Poor compliance among OTRs on sun protection and sunscreen use is documented
- Skin protection education is part of transplant clinic visits
- Ideally all patients are seen before transplantation for total body examination and treatment if needed

Sun protection education

• “SMART IN THE SUN” behavior – regular sunscreen use, protective clothing, no tanning!!!

• Self-examination for suspicious lesions is recommended, including lymph nodes for high-risk patients

• Regular follow up in dedicated dermatology clinic

“Field cancerization” and topical therapy

• Presents as extensive areas of actinic damage and profuse epidermal dysplasia histologically on sun-exposed skin
• Chronic actinic changes, keratotic and warty lesions account for increased risk of aggressive skin cancer development in OTRs
• Treatment of individual lesions fails to prevent local recurrence and new lesions occurrence
Principles of topical therapy

- Noninvasive treatment modalities are applicable to large areas of sun damaged skin
- Selectively targets premalignant cells
- Different therapeutic agents are used in cyclic rotation
- Early biopsy of any persistent lesion is strongly recommended for detecting subclinical invasion

Goals of field therapy

• Eradicate clinical and subclinical lesions
• Prevent the progression to invasive SCC
• Promote longer clinical remission until the appearance of new lesions
• Unmask subclinical deeply penetrating lesions by cleaning the background superficial changes

Topical chemotherapy

- 5-Fluorouracil, Imiquimod and Diclofenac have proven efficacy in field treatment in OTRs
- Mechanism of action is unique for every agent
- Local skin reaction is the most common side effect, ranging from mild irritation (diclofenac) to severe erythema and edema (5-FU)


Topical chemotherapy

- Treated areas are of limited size (50-60 sm²) in order to avoid severe reactions and systemic absorption
- Untreated areas in close proximity may react showing subclinical lesions
- No effects on systemic immunity or rejection episodes were observed
- Combined and sequential treatment might be considered

Results of a randomized, placebo-controlled safety and efficacy study of topical diclofenac 3% gel in organ transplant patients with multiple actinic keratosis.
Photodynamic therapy

• Uses photosensitizing topical agent and activating visible light to produce phototoxic reaction
• Substances - δ 5-aminolevulinic acid (5-ALA) & Methyl-aminolevulinic acid in different delivery forms - gel (Metvix®), liposomal formulation 5-ALA (Ameluz®)
• Light source choice depends on the thickness of the lesion, the absorption characteristics of the tissue, the wavelength and exposure time

Photodynamic therapy

• Pretreatment debridement, use of 5-ALA and red light results in better clinical response due to deeper penetration
• Pain during and after illumination is the most frequent and limiting side effect of PDT (5-ALA > MAL, red light > blue light)
• Pain management is critical for preventing patient shift; cooling, nerve blocks or day light initiation might be used

Photodynamic therapy

- PDT was found more effective than 5-FU in achieving complete resolution of lesions
- PDT was successful in treating not responsive to conventional therapy keratoses
- Whether single PDT procedure reduces the risk of new SCCs in OTRs is controversial, cyclic MAL-PDT with blue light was found protective
- Potential role of PDT in primary prevention of skin dysplasia was recently suggested

Primary Prevention of Skin Dysplasia in Renal Transplant Recipients With Photodynamic Therapy: A Randomized Controlled Trial. Togsverd-Bo K et al. Am J Transplant 2015; 27:13358
Indications for systemic therapy

• Multiple SCCs per year (5-10 /year)
• Multiple SCCs in high risk locations (eg, head and neck area)
• Explosive SCC development
• Eruptive keratoacanthomas
• Single SCC with high metastatic risk
• Metastatic SCC
• OTRs with history of lymphoma / leukemia and SCC

Systemic retinoids for chemoprevention

- Therapy does not replace surgical treatment
- Low initial dose is usually administered, then slowly increased till chemosuppression is achieved
- For effective management of side effects appropriate dosage modification and identification of individual tolerable dose are required
- Rebound effect is a rule if treatment is discontinued, often difficult to control

Capecitabine

- Prodrug of 5-FU approved for metastatic breast CA and colorectal CA
- Resolution of AK lesions noted in patients treated for those indications
- Severe drug–related toxicity in patients deficient in dihydropirimidine dehydrogenase – pretreatment screening
- Dose-related adverse effects

Role of immunosuppression in skin carcinogenesis

- Both initial induction therapy and long-term maintenance are involved in skin carcinogenesis
- Drug type and combination has major importance in skin cancer development
- Older generation calcineurin inhibitors (CNIs) and antiproliferative agents have known photosensitizing and oncogenic effect
- Patients on triple combination are at higher risk for skin cancer than on dual or monotherapy

Long-term maintenance of calcineurin inhibitor monotherapy reduces the risk for squamous cell carcinomas after kidney transplantation compared with bi- or tritherapy. Abou Ayache R et al. Transplant Proc. 2007 Oct;39(8):2592-4
mTOR inhibitors – new kid on the block

- Reasonable alternative to CNIs in selected patients
- Potent non-nephrotoxic suppressant with antitumoral and antiangiogenic properties
- Common adverse effects are hyperlipidemia and myelosuppression, sometimes proteinuria, edema, impaired wound healing
- Not recommended until stable graft function is established and surgical wounds are healed

mTOR inhibitors – continued

• NMSCs incidence reduction after switch to mTOR inhibitors was proven recently
• mTOR inhibitors are reasonable alternative for post transplant Kaposi sarcoma due to antiangiogenic effect
• Recent study failed to prove benefit of mTOR inhibitors in primary prevention of NMSCs


Revision of immunosuppression

- Considered for patients with high risk of metastases, high tumor load (more than 5-10 high-risk SCCs per year) or rare malignant tumors (melanoma, MCC)
- Revision is achieved with dose reduction or regimen change in collaboration with the transplant team
- Target is lowest level of immunosuppression which maintains good and stable graft function

Future trends

• Topical treatments – Ingenol mebutate
• Systemic prevention – Nicotinamide
• Immunosuppression – Alefacept & Alemtuzmab
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Summary

• Skin cancer development in OTRs is an increasing problem that needs proactive multidisciplinary management

• Early and frequent education on sun protection practices should be emphasized

• Regular follow up and early therapeutic intervention are cobblestones of efficient prevention

• Field therapies, systemic chemoprofilaxis and revision of immunosuppression are useful tools for skin cancer management in OTRs
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