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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

Spectrum of cancer risk among US solid organ transplant recipients Engels EA et al. JAMA 2011 Nov 2;306(17):1891-901.

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

Skin cancer in organ transplant recipients: Epidemiology, pathogenesis and management. Berg D, Otley CC. JAAD. 2002 Jul;47(1):1-17

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

Skin cancer in solid organ transplant recipients: advances in therapy and management. Zwald FO, Brown M. JAAD. 2011 Aug;65(2):253-61

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

Subsequent skin cancers in kidney and heart transplant recipients after the first squamous cell carcinoma. Euvrard S et al.Transplantation. 2006 Apr 27;81(8):1093-100.

Skin cancer education

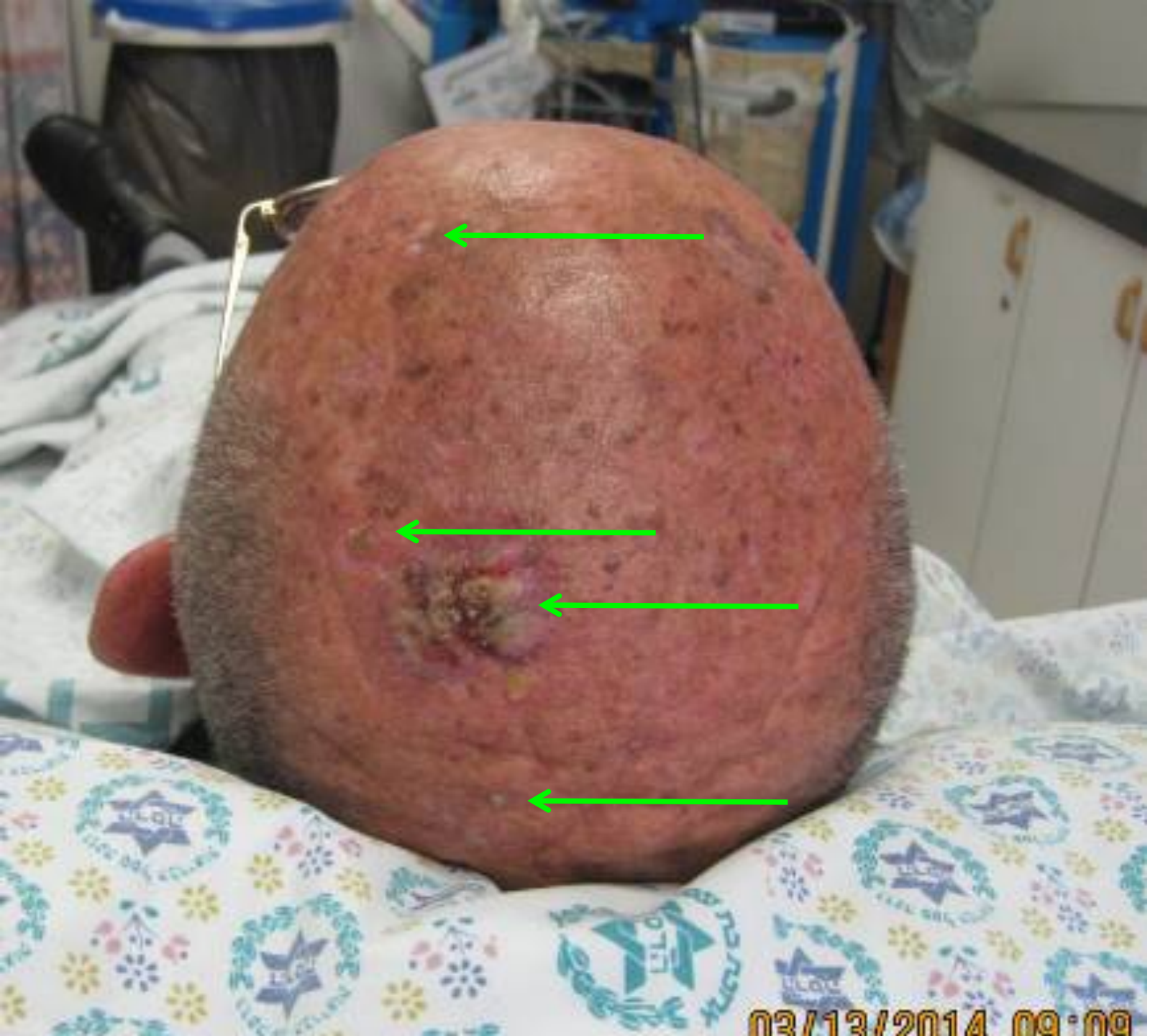
- Poor compliance among OTRs on sun protection and sunscreen use is documented
- Skin protection education is part of transplant clinic visits
- Ideally all patients are seen before transplantation for total body examination and treatment if needed

Educational outcomes regarding skin cancer in organ transplant recipients: randomized intervention of intensive vs standard education. Clowers-Webb HE et al. Arch Dermatol. 2006;142:712–8

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

Ulrich C et al. Prevention of non-melanoma skin cancer in organ transplant recipients by regular use of a sunscreen: a 24 months, prospective, case-control study. Ulrich C et al. Br J Dermatol. 2009;161:78–84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“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

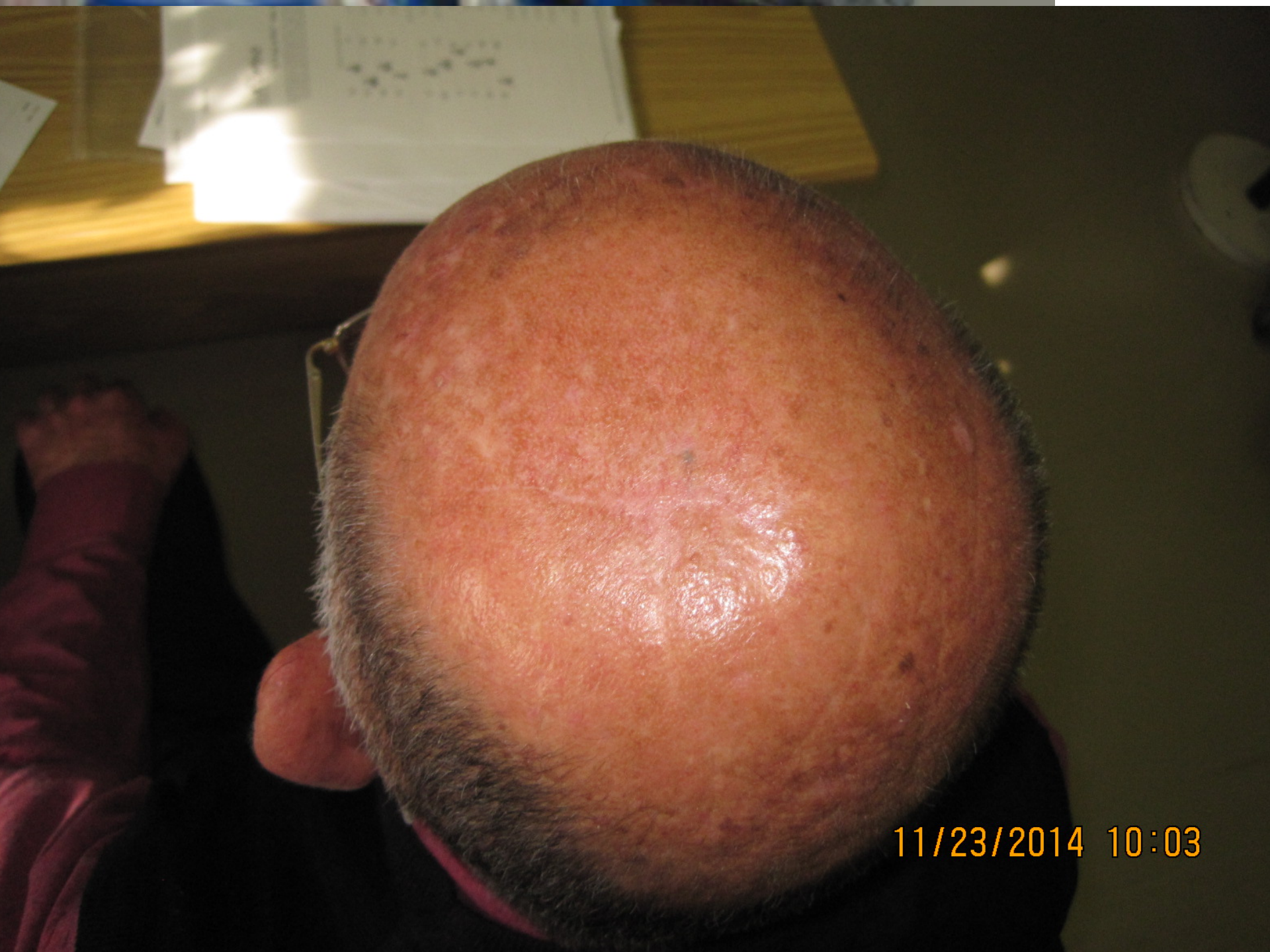
- Noninvasive treatment modalities are applicable to large areas of sun damaged skin
- Selectively targets premalignant cells
- Different therapeutic agents are used in cyclic rotation
- Early biopsy of any persistent lesion is strongly recommended for detecting subclinical invasion

Guidelines for the management of squamous cell carcinoma in organ transplant recipients. Stasko T. et al. Dermatol Surg 2004; 30:642-650.

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

Guidelines for the management of squamous cell carcinoma in organ transplant recipients. Stasko T. et al. Dermatol Surg 2004; 30:642-650.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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)

The efficacy and safety of topical 5% 5-fluorouracil in renal transplant recipients for the treatment of actinic keratoses. Ingham AI, Weightman W Australas J Dermatol 2014 Aug; 55(3):204-8

Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: randomized, double-blind, placebo-controlled trial. Brown V.L. et al. Arch Dermatol 2005; 141: 985-993

Topical chemotherapy

- Treated areas are of limited size (50-60 sm^2) 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. Ulrich C et al. Eur J Dermatol. 2010; 20(4):482-8

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

Topical photodynamic therapy of actinic keratosis in renal transplant recipients. Piaserico S. et al. Transplant Proc 2007; 39: 1847-1850

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

Topical aminolevulinic acid and aminolevulinic acid methyl ester-based photodynamic therapy with red and violet light: influence of wavelength on pain and erythema. Mikolajewska P. et al. Br J Dermatol 2009; 161: 1173-9

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

Low-dose retinoids in the prevention of cutaneous squamous cell carcinomas in organ transplant recipients. Harwood C.A. et al. Arch Dermatol 2005; 141: 456-4

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

Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. Otley CC et al. Dermatol Surg 2006; 32:562–8

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

Capecitabine to reduce nonmelanoma skin carcinoma burden in solid organ transplant recipients**.** Endrizzi B et al. Dermatol Surg 2013; 39(4):634-4

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

Sirolimus and secondary skin cancer prevention in kidney transplantation. Euvrard S et al. N Engl J Med. 2012 Jul 26;367(4):329-39

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

Kaposi's sarcoma and mTOR: a crossroad between viral infection neoangiogenesis and immunosuppression. Stallone G. et al. Transpl Int 2008; 21: 825-832.

Sirolimus use and risk of cutaneous squamous cell carcinoma (SCC) in solid organ transplant recipients (SOTRs). Asgari M.M. et al. J Am Acad Dermatol 2015; 15:1728-4.

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

Reduction of immunosuppression for transplant associated skin cancer : expert consensus survey. Otley CC et al. Br J Dermatol 2006;154:395–0

Future trends

- Topical treatments – Ingenol mebutate
- Systemic prevention – Nicotinamide
- Immunosuppression – Alefacept & Alemtuzmab
- ……

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

БЛАГОДАРЯ