# Skin Cancer Management in the Immunosuppressed Patient

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# THE STATE OF SKIN CANCER IN THE GENERAL POPULATION

- NMSC is the MC malignancy- 3.5 million in 2006
- BCC mc- 4:1 vs SCC
- MM- most fatal, approx. 10K will die in 2013
- Risk skin cancer for Immunosuppressed Pt 10-250 fold higher
- Immunosuppressed Pts have increased morbidity, mortality- multiple tumors, more agressive

# THE STATE OF SKIN CANCER IN THE GENERAL POPULATION

- Basal cell carcinoma 850,000
  - Incidence doubles every 25 years
- Squamous cell carcinoma 200,000
  - Incidence doubles every 20 years
- Melanoma 44,200
  - Incidence doubles every 15 years

# Who is Immunosuppressed?

- Transplant Patients- Organs(liver, kidney, lung, heart), BMT
- Disease management- RA, Psoriasis, IBD (TNF Inhib, prednisone)
- Diseases- HIV (lower CD4), Lymphoma (lower and impaired)
- The overwhelming majority of immunosuppressed with highest burden of disease is the Transplant Pt

# THE STATE OF TRANSPLANTATION IN U.S.

- 20,000 organ transplants per year
- 70,000-132,000 organ recipients currently alive in US
- 64,000 people awaiting transplants

# TYPES OF CANCER IN TRANSPLANT RECIPIENTS

| Cancer type | % of all tumors in transplant patients |
|---|---|
| Skin & Lip Cancer | 37 |
| Lymphoma | 17 |
| Lung | 5.6 |
| Kaposi's Sarcoma | 4 |
| Carcinoma of Uterus | 4 |
| Carcinoma of colon and rectum | 3.5 |

# Risk Factors for Skin Cancer

- UV light- DNA mutations (formation of cyclobutane pyrimidine dimers) mutations of p53 tumor suppressor
- UV immune suppression- IL-10 release, causes decrease function of APC (Langerhan's)
- HPV 5/8- E6 protein decreases apoptosis and increases cell cycle progression
- SCC of ImSup vs ImComp- 75% vs 37% had HPV DNA
- Drugs- calcineurin inhib vs mammalian target of rapamycin (mTOR) inhibitors

# PEDIATRIC TRANSPLANT RECIPIENTS

- Most at risk for lymphoma
- Skin cancer comprises 20% of all neoplasms

  (Compared with 38% in adults)
- Melanoma is more common in transplanted children, comprising 15% of all skin cancers (Compared with 5% in adults)

# POPULATION-BASED STANDARD INCIDENCE RATIOS OF SKIN CANCER IN TRANSPLANT RECIPIENTS

- Squamous cell carcinoma- 65x
- SCC of lip- 20x
- Basal cell carcinoma- 10x
- Melanoma- 3.4x

# CHARACTERISTICS OF NONMELANOMA SKIN CANCER IN TRANSPLANT RECIPIENTS

- Occur average of 30 yrs earlier
- More frequently multiple
- Increased rate of recurrence
- Increased rate of metastasis
- May have more rapid rate of growth
- May resemble warts or keratoacanthomas

# THE RISK OF SCC METASTASIS IN TRANSPLANT RECIPIENTS

- NZ/Australia Registry 7%
- Queensland pts with prior NMSC 6.5%
- Queensland pts w/o prior NMSC 3.3%
- Sydney cardiac pts 8%

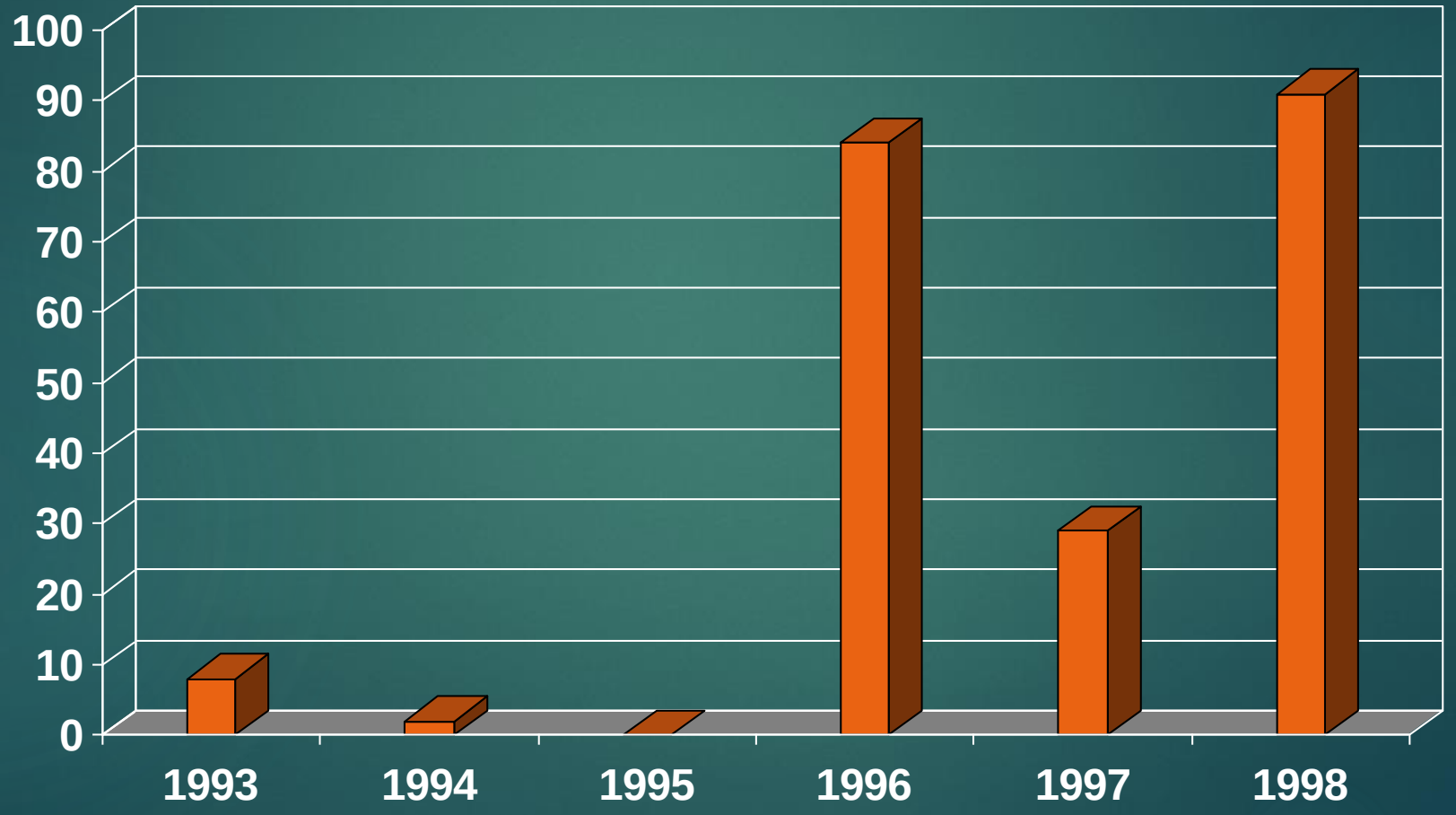
# MORTALITY FROM METASTATIC SKIN CANCER

- NZ/Aust study -> 5% overall SCC mortality
- 50% mortality in patients with melanoma
- Metastatic skin cancer (SCC, MM, Merkel Cell) accounted for 27% of all deaths after the 4th year post-transplant in Sydney

# TRANSPLANT RECIPIENTS CAN DEVELOP HUNDREDS OF SKIN CANCERS.

# 73 YEAR OLD OUTDOORSMAN S/P CARDIAC TRANSPLANT 1993

(Number of skin cancers/Year)

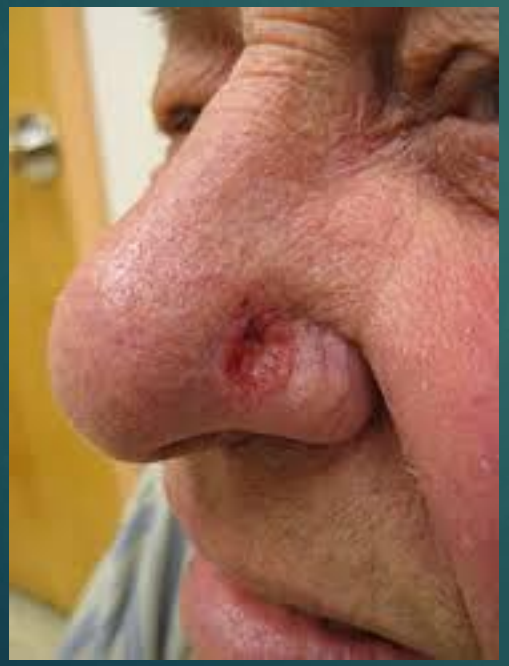


# Most Common Types of Skin Cancer

- Basal Cell Carcinoma (BCC)
- Squamous Cell Carcinoma (SCC)
- Melanoma

# BASAL CELL CARCINOMA

- Most common type of skin cancer in general population
- Appears on sun-exposed skin
- Pearly with telangectasia, may ulcerate
- Rarely metastasizes



# SQUAMOUS CELL CARCINOMA

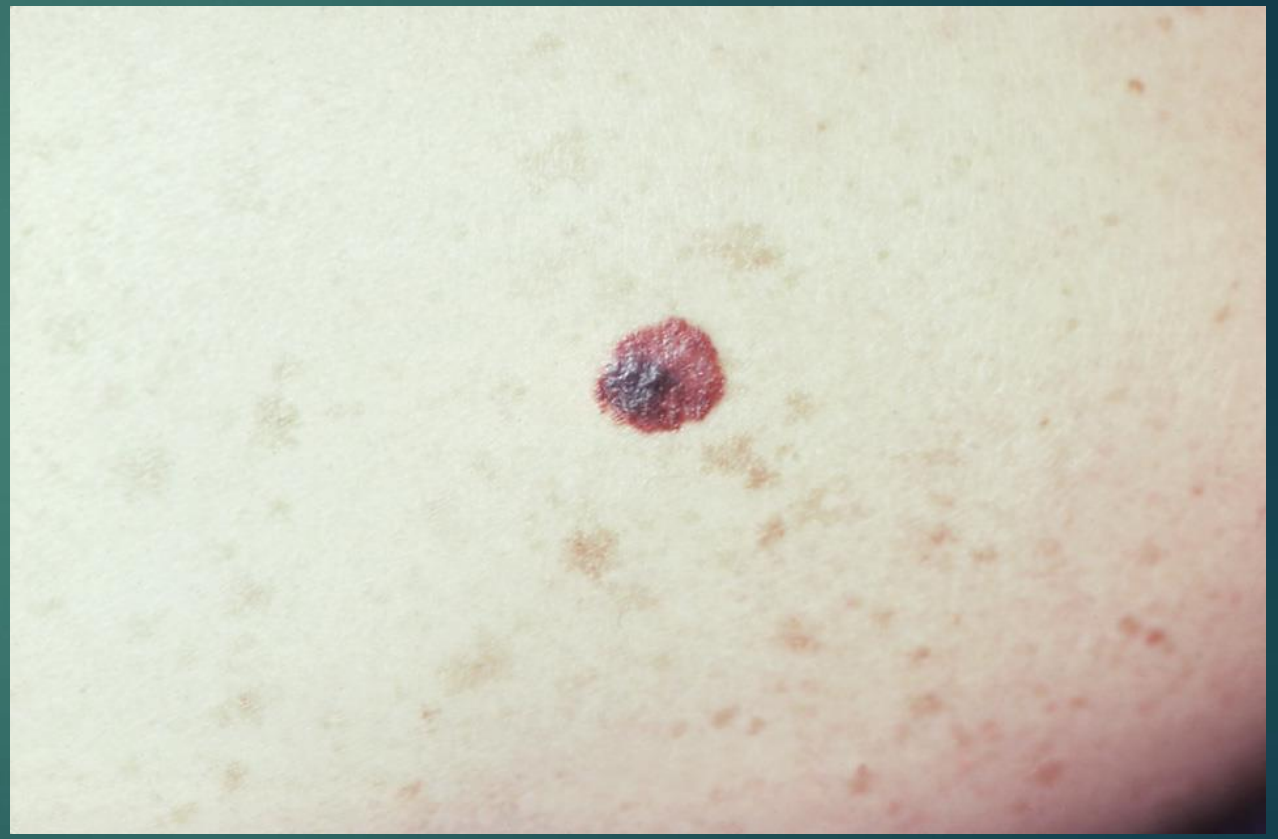
- Second most common skin cancer in the general population
- Most common skin cancer in transplant recipients
- Appears on sun-exposed skin
- Red, scaley, firm, may ulcerate
- 1-15% metastasize

# ACCELERATED CARCINOGENESIS: THE LIFE CYCLE OF DYSPLASIA

- Actinic damage
- Actinic keratosis
- Squamous cell carcinoma in situ
- Invasive squamous cell carcinoma
- Metastatic squamous cell carcinoma

# MELANOMA

- Bad type of skin cancer, "Mole Cancer"
- Appears on sun-exposed and non-sun exposed skin
- Asymmetry, Border Irregularity, Color variation, Diameter greater than 6 mm
- Rate of metastasis depends on depth of tumor into skin- Breslow depth



# IMMUNOSUPPRESSIVE AGENTS

- Corticosteroids
- Azathioprine (Imuran)
- Cyclosporine
- Tacrolimus (FK506)
- Rapamycin (Sacrolimus)
- Mycophenolate (Cellcept)
- Antilymphocyte antibodies

# Calcineurin Inhibitors

- Cyclosporin
- Tacrolimus (FK506)
- Decreases activation of IL-2; decrease T-cell activation

# mTOR Inhibitors

- Sirolimus (Rapamune)
- Everolimus
- Inhibition of mTOR- inhib IL-2, no T or B-cell activiation

# mTOR vs Calcineurin Inhib

- NEJM Study Siro vs Cal Inhib- Kidney transplant with at least 1 SCC
- 64 Pts switched to Siro, 56 Pts stay on Cal Inhib
- SCC free survival at 2 years- Siro 78%, Cal inhib 61%
- Majority of Siro Pts with increased AE (edema, acne mc)
- Serious AE- 60 vs 14 (pneumonitis, diarrhea)
- 23% D/C Siro tx
- Can consider switching if Pt developing SCCs

# Purine Synthesis Inhibitors

- Azathioprine
- Mycophenolate mofetil
- No AZA vs Low dose AZA (3x SCC) vs High dose AZA (6x SCC)
- AZA has selective UVA sensitivity- oxidative stress, DNA mutations
- Heart Transplant Study- Cal inhib w/ MFF or AZA
- MMF asso w/ lower risk of malignancy- 0.73 relative risk

# NMSC and TNF Inhibitors

- 5 year F/U study of RA showed no increase in SCC
- TNF and IBD- may have slight increase for NMSC and MM- pts have also been on other drugs (azathioprine)
- RA vs OA- RA showed slight increase for NMSC
  - Increase asso w/ prednisone and TNF w/ MTX

# Voriconazole and Lung Transplant

- Antifungal used for prophylaxis
- 2.6 fold increase risk for SCC
- Risk increases with dose- 5.6% per 60 day dose (200mg BID)
- Thought to act as a photosensitiver

# THE OPTIMAL MANAGEMENT OF ORGAN TRANSPLANT RECIPIENTS AT RISK FOR SKIN CANCER

- Pre-transplant evaluation
- Risk assessment
- Education
  - Prevention/recognition/skin exam
- Preventative therapies
- Coordination of care- primary, transplant, derm, onc

# RECOGNITION OF THE HIGH-RISK PATIENT

- Fair or easily burned skin
- Blue, green or hazel eyes
- Red or naturally blonde hair
- Extensive freckling
- History of extensive outdoor sun exposure
- A prior history of skin cancer
- A family history of skin cancer

# NECESSARY ACTION FOR PREVENTION OF SKIN CANCER

- Sun Protection
- Once a month self skin examination
- Examination by a dermatologist if risk factors warrant
- Treatment of precancers and cancers early

# SUN PROTECTION

- Wear broad spectrum sunscreen with >/= SPF 30
- Look for sunscreen in daily moisturizer and make-up if worn
- Limit out-door activities between 10AM & 4PM
- Wear protective clothing
- Wear a broad-brim hat
- Avoid natural & artificial tanning

# SUNSCREEN

- Block UVA/UVB - complete block, TiOx and ZiOx
- SPF 30 or greater
- Apply liberally
- Reapply every 2 hours (no matter what the bottle advertises)

# PROTECTIVE CLOTHING

- Long sleeve shirt
- Long pants
- Tight weave fabric
- Special clothes with SPF available
- Special detergents available to give SPF to clothes
- Broad-brimmed hat
- Tan is NOT protective!

# MONTHLY SELF SKIN EXAMINATION

- Well lit room
- Two mirrors
- Family member to help
- Look at all skin surfaces
- Early detection is key

# WHAT TO LOOK FOR?

- Persistent red areas
- Areas with persistent sandpaper like scale
- Persistent sores/Won't heal
- Areas that bleed easily
- Spots that change colors
- ABCD guidelines for moles

# ABCDE GUIDELINES

- A - Asymmetry
- B - Border irregularity
- C - Color variation
- D - Diameter greater than 6mm (size of a pencil eraser)
- E – Evolution/Elevation
- Ugly duckling

# Topical Medications to Provide Prevention and Treatment

- Topical Retinoids- data suggests not protective
- Topical 5-fluorouracil (Efudex, Carac)
- Topical Imiquimod (Aldara, Zyclara)
- Photodynamic Therapy- uses topical Levulan with Blue Light
- Repeated use and combinations
- Lesion treatment vs Field treatment

# Topical 5-FU- Efudex, Carac

- 5-FU inhibits Thymidylate synthase inducing apoptosis in rapidly dividing cell
- Skin becomes inflamed, crusted, may ulcerate
- Challenge to control reaction- TCS (TAC, Clobet)
- Efudex BID x 2-4 weeks, sometimes longer
- Carac daily 2-4 weeks
- Chemowraps- weekly Efudex under Unna wrap occlusion
- Works well for extremities
- Response rates- 60-80%

# 5-FU Skin Reaction

# Topical Imiquimoid

- Aldara 5% cream
- Zyclara 3.75%
- Immunomodulator- activates toll like receptors, creates antitumor cellular immune response
- Similar response and efficacy to 5-FU
- Hyperkeratotic lesions usually more resistant- if lesion remains, consider Bx

# Oral Prevention/Treatment

- Capecitabine- prodrug of 5-FU
- Low doses given in 2-3 week cycles
- Reduces AK and SCC, not BCC
- No rebound of tumor growth when stopped
- Given on Onc- monitoring labs
- SE- fatigue, diarrhea, oral ulcers, hand/foot syndrome

# Oral Prevention/Treatment

- Acitretin- systemic retinoid
- Supresses carcinogenesis via regulation of cell promotion (not transformation)
- Start low dose and titrate up
- Rebound occurs when stopped
- Monitor Labs- Lipids (TG elevation), CBC, LFT
- SE- dryness- lips, nose, skin
- Used if developing 10+ SCC year

# Oral Prevention/Treatment

- Cetuximab- inhibitor of EGFR
- SCC overexpress EGFR
- Used for mets or unresectable SCC
- MC SE is acne type rash
- Can also consider adjustment of Pts immune drugs if Pt unresponsive or has a high tumor burden

# Photodynamic Therarpy (PDT)

- AKA as Blue Light (Dusa)
- Apply aminolevulinic acid to area of treatment
- Incubate 1-3 hours, ALA is converted to protoporphyrin IX w/in the cells
- Expose to wavelength of light (415 nm- visible light spectrum)
- Light exposure time approx. 16 min
- Produces a ROS and destruction of the cell
- Red light available in Europe- longer wavelength= deeper penetration into the skin

# Photodynamic Therapy

# Surgical Management

- Liquid Nitrogen
- EDC (scrape and burn)
- Wide Excision/Mohs Surgery
- Treat with topicals aggressively, remaining lesions get surgical treatment
- Overall goal is tissue conservation

# HOW INFORMED ARE THE TRANSPLANT RECIPIENTS?

- UK survey
- 91% know sun is harmful
- 77% know immunosuppression makes worse
- 69% used sun precautions
- 43% used sunscreen
- 10% used ≥ SPF 10

# When SCC goes BAD


# When SCC goes BAD


# When SCC goes BAD



Mohs surgery never completed due to multiple in-transit mets on Mohs sections.  Graft placed and Pt set up for Adjuvent Tx (chemo, radiation)
Pt expired by the end of January.

# International Transplant Skin Cancer Collaborative

- ITSCC website
- http://www.itscc.org/
- Good resource for Pts and physicians.

# Thank You