MINI-SYMPOSIUM

Cutaneous Oncology- NMSC

• Actinic Keratoses– New & Old Therapies
• BCC & SCC: Different Cancers-Different Treatments

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CUTANEOUS ONCOLOGY: NMSC

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Actinic Keratoses--New & Old Therapies
Actinic Keratoses: Definition

Cutaneous neoplasms composed of proliferations of cytologically aberrant, epidermal keratinocytes......caused by prolonged exposure to ultraviolet radiation

......that are the initial lesions in a disease continuum that progresses to squamous cell carcinoma

PRECURSOR LESIONS!
Actinic Keratoses: Clinical Characteristics

• Appearance:
  – Typically erythematous subtle scaly papule
  – Gen’l ~ 5mm...vary 1mm to > than 1 cm
  – Many identified by palpation (tactile roughness) *
  – Non-indurated!

• Location
  – ≥80% occur head, neck, & arms

• Symptoms:
  – Itchiness, burning, tenderness

*Pts. may have 3 to 10 times more subclinical lesions than visible clinical lesions
Actinic Keratoses: Clinical Presentations

• Typical presentation:
Actinic Keratoses: Clinical Presentations

• Common varieties:

- Hyperkeratotic
- Cutaneous horn
- Atrophic
- Pigmented
Actinic Keratoses: Clinical Presentations

• Unique clinical types:

Actinic Cheilitis
Actinic Keratoses: Clinical Presentations

BIOPSY!

INDURATION = MALIGNANT
Actinic Keratoses: Precursors of SCC

• Multiple studies showed
  – 60% of SCCs arose from AK lesions
  – In 444 of 459 (97%) SCCs examined, there was a contiguous AK

Actinic Keratoses: Marker of SCC Risk

<table>
<thead>
<tr>
<th>No. of AKs</th>
<th>Relative Risk*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>1-5</td>
<td>1.7</td>
<td>(0.4, 6.5)</td>
</tr>
<tr>
<td>6-20</td>
<td>4.2</td>
<td>(1.1, 16.1)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>11.0</td>
<td>(2.6, 46.6)</td>
</tr>
</tbody>
</table>

- Patients with more AKs have a greater risk of developing SCC

*Relative risk of SCC for each category (number of AKs) calculated as incidence rate within that category divided by rate in reference category (0 AKs), after adjusting for corresponding age and sex distribution of the world population.

Actinic Keratoses: Precursors of SCC

• How often does a SCC arise from a pre-existing AK?
  - 1986 Marks et al\(^1\) determined yearly incidence rate of an AK transforming to SCC in persons with multiple AKs (ave. 7.7 lesions) was approximately 0.24%.
  - 1988 Marks et al\(^2\) determined transformation rate per lesion/year (ave. 8.4 lesions) 0.075%.
  - 2009 Criscione et al\(^3\) determined 1-year risk of an AK progressing to an invasive or in situ primary SCC was 0.60%, while the risk after 4 years was 2.57%.

UV Light a “Complete Carcinogen”

Initiation
Mutant Cells
- Pyrimidine dimers DNA & RNA
- p53 suppressor gene

Promotion
Actinic Keratoses
- Ha-ras oncogene

Progression
Skin Cancer
- P16 INK4a suppressor gene

Immunosuppression
Actinic Keratoses: Precursors of SCC

Changes Indicative SCC

Sources: Jerant et al, 2000; Sober, Burstein, 1995
## Actinic Keratoses: Treatment

<table>
<thead>
<tr>
<th>Lesion Targeted</th>
<th>Field Directed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryosurgery</td>
<td>Imiquimod*</td>
</tr>
<tr>
<td>Electrodessication &amp; curettage</td>
<td>5-Fluorouracil (5-FU)*</td>
</tr>
<tr>
<td>PDT: Conventional*</td>
<td>Diclofenac*</td>
</tr>
<tr>
<td></td>
<td>Ingenol Mebutate*</td>
</tr>
<tr>
<td></td>
<td>Chemical Peels</td>
</tr>
<tr>
<td></td>
<td>Laser Ablation</td>
</tr>
<tr>
<td></td>
<td>Retinoids</td>
</tr>
<tr>
<td></td>
<td>PDT: Modified</td>
</tr>
</tbody>
</table>

*FDA approved*
Actinic Keratoses: Treatment

Lesion Targeted Modalities

- Cryosurgery (liquid nitrogen)
- Conventional Photodynamic Therapy (PDT)
- Electrodissection & Curettage

Debridement of Hyperkeratotic Lesions!

Actinic Keratoses: Treatment

Lesion Targeted Modalities

• Cryosurgery (LN$_2$): *Is touted cure rate accurate?*

  – 1982 Lubritz RR & Smolewski SA$^1$: CR$= 98.8\%$

    • Retrospective F/U study; Methods “loose”; No photos
    • F/U minimum 1 yr--maximum 8.5 yrs
    • 1018 lesions treated on 70 pts
    • Hand held unit-direct open-spray technique
    • Variable freeze times-- *thaw time 20-45 seconds!*
    • AEs not addressed!

Actinic Keratoses: Treatment

Lesion Targeted Modalities

• Cryosurgery (LN$_2$): *Is touted cure rate accurate?*
  
  – 2004 Thai K et al$^1$ (Australia): Overall CR = 67.2%
    
    • Prospective multi-center study
    
    • **Single timed F/T cycle with 1-2 mm margin** (Freeze time defined as time from formation of an ice-ball to the commencement of thawing)
  
  – Conclusions:
    
    • **Freezing times 10-15 sec* → optimal risk/benefit balance**
    
    • Success dependent on duration of freezing
    
    • **Hypopigmentation 29% (related freezing time)**

$^1$Thai K et al. Intl J Dermatol 2004; 43:687-692
Actinic Keratoses: Treatment

Lesion Targeted Modalities

- Cryosurgery (Liquid Nitrogen)
  - Common adverse events³
    - Pain & edema
    - Blistering, crusting, erosion/ulceration
    - Infection
    - Lesional hypopigmentation
    - Peripheral hyperpigmentation
    - Scarring

Actinic Keratoses: Treatment

Rationale for “Field Directed” Therapies

• Noninvasive
• Potentially reduces risk for scarring
• Ideal for difficult-to-treat locations
• Cost
• Reconciliation of subclinical “field cancerization”
• Secondary “cosmetic benefit”
Actinic Keratoses: Field Cancerization

• Defining the Concept
  • Conceived by Slaughter in 1944¹
  • Term introduced 1953² as histologically altered mucosa surrounding tumors removed from the upper GI tract
  • Definition changed to include an area which is *clinically occult* but has *multifocal pre-neoplastic changes*, showing *genetic mutations*, & which precedes the development of second primary tumors & local recurrences
  • Phenomenon has been described in oropharynx, esophagus, stomach, lung, colon, anus, cervix, bladder & SKIN!

¹Slaughter DP. Int Abstr Surg 1944179:89-98
²Slaughter DP et al. Cancer 1953;6:963-8
Actinic Keratoses: “Field Cancerization”
Actinic Keratoses: Treatment “Field Directed” Treatment Options

- **5-Flurouracil** 0.5%, 1%, 2%, 5% cream/solution
- **Imiquimod** 2.5%, 3.75%, 5% cream
- **Diclofenac** 3% gel
- **Ingenol Mebutate** 0.015% & 0.05% gel
- PDT (adapted)*
- Retinoids*
- Chemical peels*
- Laser resurfacing (CO2/Erbium-Yag)*

* “Off Label”
Actinic Keratoses: Treatment

Older “Field Directed” Options

5-FLUOURACIL
ANTIMETABOLITE
Inhibits DNA synthesis by thymidylate synthetase (cytotoxic effect)

IMIQUIMOD CREAM
IMMUNE RESPONSE MODIFIER
Activation of innate immune response & cytokines
Up-regulation of CMI response

DICLOFENAC GEL
NSAID Cox II inhibitor
Cyclooxygenase inhibition
AKs: Efficacy Rates

FDA Registration Studies

- 5% 5-FU solution
- 0.5% 5-FU (porous microsphere) cr
- 2.5% imiquimod cr
- 3.75% imiquimod cr
- 5.0% imiquimod cr
- 3% diclofenac gel
- 0.015% ingenol mebutate gel (face & scalp)
- 0.05% ingenol mebutate (trunk & extremities)
- 5 ALA PDT (conventional “lesion directed”)

86% of treated lesions had CR
58% pts with 100% clearing
31% pts with 100% clearing
36% pts with 100% clearing
45% pts with 100% clearing
47% pts with 100% clearing
42% pts with 100% clearing
34% pts with 100% clearing
77% pts with 100% clearing
Actinic Keratoses: Treatment

5-FU Clinical Responses

Seek & Destroy

Irritant reaction
Actinic Keratoses: Treatment
Newer Topical 5-FU Cream (Carac™ 0.5%)

- Carac™ 0.5% cream
  - 0.5% fluorouracil, (0.35% in porous microsphere)
  - Once-daily application for 4 weeks as tolerated
  - 58% of patients had 100% clearing at 4 weeks
  - 2-week healing period post treatment

Indication: Treatment of multiple actinic keratoses
FACE & ANTERIOR SCALP

Actinic Keratoses: Treatment

Comparative Mean Plasma 5-FU Concentrations

Plasma 5-FU Concentration (ng/mL)

Predose  1  2  3  4  6  8  10  12  16  24

Hours After Dosing

Carac™ Cream, 0.5% (n=1)
Fluorouracil Cream, 5% (n=6)
Actinic Keratoses: Treatment

Imiquimod Cream, 5% (Aldara ™)

• Apply BIW x 16 weeks HS
• Limited 25 cm²
• **45% had 100% clearance 8 weeks post Rx**
  • 83% median percent reduction in number of AKs from baseline
• Heal in 1-2 weeks

Indication: Treatment of actinic keratoses

FACE OR SCALP

Actinic Keratoses: Treatment

*Imiquimod Cream, 2.5% or 3.75% (Zyclara™)*

**Identifying Medical Needs**

- **Expanded Treatment Area**
- **Maintained Efficacy**
  - >25 cm²
  - <16 weeks

- **Simplified Dosing Regimen**
- **Shortened Treatment Time**

Once daily
Actinic Keratoses: Treatment

*Imiquimod Cream, 2.5% or 3.75% (Zyclara™)*

**AK Lesions Revealed & Treated**

86% of subjects (3.75%) had previously undetected AK lesions revealed

Actinic Keratoses: Treatment
*Imiquimod Cream, 2.5% or 3.75% (Zyclara™)*

<table>
<thead>
<tr>
<th>Strength</th>
<th>3.75% Imiquimod</th>
<th>2.5% Imiquimod</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Complete Clearance</td>
<td>35.6*</td>
<td>30.6*</td>
<td>6.3</td>
</tr>
<tr>
<td>% Partial Clearance</td>
<td>59.4</td>
<td>48.1</td>
<td>22.6</td>
</tr>
<tr>
<td>% Lesion Reduction</td>
<td>81.8</td>
<td>71.8</td>
<td>25</td>
</tr>
</tbody>
</table>

*In a previous study of 5% imiquimod 2x/week for 16 weeks, complete AK clearance was achieved in 45.1% of subjects.\(^3\)

*Statistically significant from placebo, \(P < .001\)

1. Data on file. Graceway Pharmaceuticals, LLC.
2. Swanson N, et al. 12th World Congress on Cancers of the Skin; May 3-6, 2009; Tel-Aviv, Israel; poster.
Actinic Keratoses: Treatment

Imiquimod Cream, 2.5% or 3.75% (Zyclara™)

Dosing

• Apply 1-2 packets to face or balding scalp
  – Depends on severity and size treated
• Script comes with 28 sachets*
  – Sufficient for full course of 2-2-2 if 1 packet/application
• 36% (3.75%) & 31% (2.75%) had 100% Clearance

*NOW AVAILABLE (28 applications) PUMP DISPENSER: 1 Plunge = 1 SACHET

Indication: Treatment of actinic keratoses

FACE OR SCALP
Actinic Keratoses: Treatment

*Diclofenac Sodium Gel, 3% (Solaraze™ Gel)*

- First in a new class of AK therapy
- Contains a nonsteroidal anti-inflammatory drug (NSAID)
- NSAID a Cox II inhibitor

Actinic Keratoses: Treatment

*Diclofenac Sodium Gel, 3% (Solaraze™ Gel)*

**Prostaglandins**

😊 COX I → Necrosis

💥 COX II → Neoplasia

Goldyne ME. *Prostaglandins Other Lipid Mediat.* 2000.
Actinic Keratoses: Treatment

*Diclofenac Sodium Gel, 3% (Solaraze™ Gel)*

- Apply twice daily 60-90 days
- **47% patients had 100% clearing post Rx**
- 19% had 100% clearing with vehicle

**Indication:** Treatment of actinic keratoses

**NOT SITE SPECIFIC**
Actinic Keratoses: Treatment Photodynamic Therapy (PDT)-The Concept

1. Generation of photosensitizer
   – Application of prodrug (5-Aminolevulinic Acid)
   – Accumulation of endogenous photosensitizer (Pp IX)

2. Activation of photosensitizer
   – Application of light (Blue U 417-432nm)
   – Presence of O₂
   – Generation of Reactive O₂ Species (ROS)

3. Cell Death
   – Necrosis/apoptosis

Szeimies RM et. al., Acta Derm Venerol 2005;85: 483-490 (review article)
Actinic Keratoses: Treatment

**PDT-Activation of photosensitizer**

Reactive Oxygen Species Generated from Light-activated PpIX

- 5-Aminolevulinic Acid (ALA)
- ALA → O₂ → PpIX → ROS

Actinic Keratoses: Treatment
PDT-Protoporphyrin IX Absorption Spectrum

Actinic Keratoses: Treatment:

PpIX absorption in vivo

BLU-U, ClearLight 417 - 432 nm
Actinic Keratoses: Treatment
Photodynamic Therapy (Levulan Kerastick®)
Actinic Keratoses: Treatment

*Photodynamic Therapy (Levulan Kerastick®)*

BLU-U®  Blue Light Photodynamic Therapy Illuminator

417-432nm
Actinic Keratoses: Treatment

Photodynamic Therapy (Levulan Kerastick®)

• Adapted “Short contact-field directed” PDT regimen
  – Touma D et al* applied 5-ALA to “broad area” for 1, 2 or 3 hours followed by 10 J/cm² (1000 seconds) Blu-U light (rather than FDA approved “spot treatment” with 12-14 hrs incubation)
  – Results:
    • Incubation time difference insignificant
    • Clearance similar to pivotal FDA studies
    • Improved cosmesis
    • Authors opined “better tolerated” than 5-FU

USF: We apply 2 hours

Novel Technology for Next Generation PDT
ALA in Ameluz® is stabilized by the nanoemulsion BF-200

Unstable ALA is stabilized by BF-200

- Shelf life of 24 months
- No refrigerated transport necessary
- Open stability of 3 months
- Refrigerated long-term storage
BF-200 ALA Nanoemulsion: Structure & Composition

Electrostatic interaction between the Active Pharmaceutical Ingredient (5-aminolevulinic acid, or API) and lecithin

5-aminolevulinic acid (API)
Ameluz (10% ALA) gel: Clinical Benefits

- Optimized 5-ALA transport across the stratum corneum
- Improved skin penetration
  - Down to the basal membrane of epidermis
- No systemic absorption
- Easy and localized application
- 2g tube can treat entire face

Maisch T et al. Experim Dermatology; 2009.
AKs: Ingenol Mebutate

• Sap of plant *Euphorbia peplus* - a traditional remedy for skin disorders, Aks & BCC
• “Milkweed,” “Petty surge” or “Radium weed”
• Active constituent ingenol-3-angelate (hydrophobic dipertene ester)

AKs: Ingenol Mebutate

- Preclinical studies indicate that PEP005 gel has a dual MOA$^{1,2}$
  1. **Rapid, direct cell necrosis** & cell death (Initial chemoablation by disruption of the plasma membrane & loss of mitochondrial membrane)
  2. **Specific protein kinase C–modulated tumor cell apoptosis**, & neutrophil-mediated, tumor-specific, antibody-dependent cytotoxicity
- 1°necrosis as MOA..........................makes it unlikely for development of apoptosis resistance in tumor cells

Actinic Keratoses Treatment:  
*Ingenol Mebutate Gel 0.015% & 0.05% (Picato®)*

• Indication: Age 18 or older
  – Face & Scalp:
    • Apply 0.015% gel once daily 3 consecutive days
  – Trunk & extremities:
    • Apply 0.05% gel once daily 2 consecutive days

• AEs ≥ 2% :
  – Local skin reactions
  – Application site pain, pruritus, irritation & infection
  – Perioribital edema
  – Nasopharyngitis & headache

Actinic Keratoses Treatment: Ingenol Mebutate Gel 0.015% & 0.05% (Picato®)

• Efficacy: (Determined @ day 57)
  – Face & scalp:
    • CC Study # 1 = 37%; Study # 2 = 47%
    • PC Study # 1 = 60%; Study # 2 = 68%
  – Trunk & extremities
    • CC Study # 1 = 28%; Study # 2 = 42%
    • PC Study # 1 = 44%; Study # 2 = 55%

Actinic Keratoses Treatment:
*Ingenol Mebutate Gel 0.015% & 0.05% (Picato®)*

• How Supplied:
  – Clear colorless gel supplied in UNIT DOSE TUBES
    • 0.015% 3 doses/carton (face & scalp)
    • 0.05% 2 doses/carton (trunk & extremities)
  – Must Keep refrigerated!
  – Let dry 15 minutes after application
  – Avoid excessive sweating 6 hours s/p application
  – Wash off after 6 hours

Actinic Keratoses: Treatment Summary

- Actinic keratoses are *precursors of SCC* ............thus.................. *a need to treat!*
- Many treatment options--*All are valuable!*
- Cryosurgical destruction "gold-standard" discrete lesions
- The concept of "*field cancerization*" cannot be discounted
- All patients deserve consideration for "*field treatment*"
- "*Field treatment*" can be useful ADJUNCT to lesion directed modalities like cryosurgery
BCC/SCC
Different Cancers
Different Treatments
Nonmelanoma Skin Cancer

Genetic Risk Factors

• High risk phenotype
  – Fair skin, light hair, blue eyes, Celtic ancestry

• Basal Cell Nevus Syndrome (Gorlin)
  – Auto dom (defect patched \textit{PTC} tumor suppressor gene)
  – Innumerable lesions
  – Jaw cysts & skeletal abnormalities
  – Ocular hypertelorism
  – Palmoplantar pits
  – CNS tumors (medulloblastoma)
Nonmelanoma Skin Cancer

SCC: Etiology

- Chronic cumulative ultraviolet exposure
- Chronic radiodermatitis
- Old thermal burn scars
- Topical carcinogens
- Chronic inflammation
- Chronic HPV infection
- Antecedent inorganic arsenic ingestion

All have precursor lesions—*keratoses*
Nonmelanoma Skin Cancer

SCC: Etiology

- Chronic cumulative ultraviolet exposure
Nonmelanoma Skin Cancer

*SCC: Etiology*

- Chronic radiodermatitis
Nonmelanoma Skin Cancer

SCC: Etiology

- Chronic inflammation

Vaccination site
Nonmelanoma Skin Cancer

SCC: Etiology

- Chronic HPV infection

Carcinoma cuniculatum

Buschke-Loewenstein

Verrucous Carcinoma (HPV 6,11,16,18)
Nonmelanoma Skin Cancer

SCC: Etiology

• Inorganic arsenic ingestion

Bowen’s disease

Arsenical keratoses
Nonmelanoma Skin Cancer

**SCC: Etiology**

- **Inorganic arsenic ingestion**
  - **Source:** medicinals, contaminated water, weed killers, fungicides, sheep dip
  - **Clinical**
    - Punctate palmoplantar arsenical keratoses (precursors)
    - Multiple NMSC (actinic & non-actinic)
    - Distinctive lesions (Bowen’s & sBCC)
  - Associated with internal malignancy (GI & pulmonary)
Nonmelanoma Skin Cancer

SCC: Risk of Metastasis
Nonmelanoma Skin Cancer

**SCC: High Risk Lesions**

- Large lesions (> 2 cm)
- Deeply invasive
- Affects bone, muscle, nerve
- Poorly differentiated
- Sparse inflammation
- Immunosuppression
- Arising from scar
- Location “H” zone
  - Esp. lip & ear
Nonmelanoma Skin Cancer

**SCC: Treatment**

- **Destruction**
  - SCC in situ
    - **Physical**: Cryosurgery (double freeze-thaw) or curettage & desiccation
    - **Medicinal**:
      - 5% 5-FU BID 12 weeks
      - 5% Imiquimod cream 5X week X 6 weeks (“Off label”)
  - Well differentiated SCC extremities very elderly
    - Curettage & desiccation

- **Conventional excision**
  - Standard procedure (4mm margin)
  - **If “flap” closure anticipated use frozen section control!**

- **Radiation**
  - Elderly
  - Auditory canal
  - Adjunctive therapy (perineural involvement or residual disease)

- **Mohs micrographic surgery**
  - Special indications only
Nonmelanoma Skin Cancer

*SCC: Treatment*

- Conventional surgery technique
Nonmelanoma Skin Cancer

SCC: Treatment

- Mohs micrographic surgery technique
Nonmelanoma Skin Cancer

**SCC: Treatment**

- Mohs micrographic surgery indications
  - Recurrent or large lesions
  - Ill-defined margins
  - Deeply infiltrative or involving nerves, muscle or bone
  - High recurrence rates (e.g. H-zone, nailbed)
  - Tissue conservation necessary (e.g. nose, eyelid)
  - Past radiation or lesion arising in scar
  - Verrucous carcinoma
  - Immunosuppressed patient
Nonmelanoma Skin Cancer

*BCC: Clinical Types*

- Nodulo-ulcerative
- Pigmented
- Superficial (erythematous) multicentric
- Morphea-like
Nonmelanoma Skin Cancer

*BCC: Clinical Types*

- Nodulo-ulcerative
Nonmelanoma Skin Cancer

*BCC: Clinical Types*

- Nodulo-ulcerative
Nonmelanoma Skin Cancer

BCC: Clinical Types

• Nodulo-ulcerative
Nonmelanoma Skin Cancer

*BCC: Clinical Types*

- Nodulo-ulcerative

Giant Lesions = *metastasis*
Nonmelanoma Skin Cancer

*BCC: Clinical Types*

- Pigmented
Nonmelanoma Skin Cancer

**BCC: Clinical Types**

- Superficial (erythematous) multicentric
Nonmelanoma Skin Cancer

**BCC: Clinical Types**

- Morphea-like
Nonmelanoma Skin Cancer

**BCC: Treatment**

- **Destruction**
  - **Physical:** Curettage & Desiccation (common)
  - **Medicinal:** Superficial ONLY!
    - 5% 5-FU or 5% imiquimod cream

- **Conventional excision**
  - Standard procedure (4mm margin)
  - **If flap anticipated-frozen section control!**

- **Radiation**
  - When surgery contraindicated
  - Post-surgical adjunct
    - Residual disease or perineural invasion

- **Mohs micrographic surgery**
  - Special indications only
Nonmelanoma Skin Cancer
Superficial BCC: Treatment

• 5-FU Cream or solution, 5% (Efudex®)
  – Indications:
    • *Superficial* basal cell carcinoma
    • When conventional methods are impractical
      ▪ Multiple lesions
      ▪ Difficult treatment sites
    • Biopsy diagnosis should be established
    • For isolated, easily accessible lesions-- surgery is preferred “since success is almost 100%”
Nonmelanoma Skin Cancer
Superficial BCC: Treatment

• 5-FU Cream or solution, 5% (Efudex®)
  – Dosage & administration:
    • Apply BID sufficient amount cover lesion
    • Treat 3-6 weeks -- may require 10-12 weeks
    • Pt followed a reasonable time to determine if cure
  – Efficacy
    • 93% complete response
Nonmelanoma Skin Cancer
Superficial BCC: Treatment

- **Imiquimod Cream, 5% (Aldara™)**
  - Indications:
    - Biopsy documented primary *superficial* BCC
    - Immunocompetent adults
    - Maximum diameter 2 cm
    - Trunk (excluding anogenital), neck, & extremities (excluding hands/feet)
    - Only when surgical methods are less appropriate
    - Only if patient follow-up can be reasonably assured
Nonmelanoma Skin Cancer
Superficial BCC: Treatment

- **Imiquimod Cream, 5% (Aldara ™)**
  
  - Dosage & administration:
    - Apply daily HS 5X/wk X 6 wks—wash off after 8 hrs
    - Apply one drop to lesion & surrounding 1 cm skin
    - Rest period allowed if too inflamed
    - Reassess when local inflammation resolved (~ 12 weeks post-treatment)

  - Efficacy
    - 75% Clinically & histologically clear

Nonmelanoma Skin Cancer

BCC: Treatment

• Mohs micrographic surgery indications
  – Recurrent or large lesions (>2 cm)
  – Ill-defined margins
  – Deeply invasive lesions
  – Aggressive histologic pattern (morphea-like)
  – Tissue conservation necessary e.g. nose & eyelids
  – High recurrence rates (“H” zone)
## Nonmelanoma Skin Cancer

### 5 Year Cure Rates

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>BCC</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional excision</td>
<td>89.9</td>
<td>91.9</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>91.3</td>
<td>90.0</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>92.5</td>
<td>NA</td>
</tr>
<tr>
<td>Desiccation &amp; curettage</td>
<td>92.3</td>
<td>96.3</td>
</tr>
<tr>
<td>Mohs micrographic</td>
<td>99.0</td>
<td>96.9</td>
</tr>
</tbody>
</table>

NA - Data not available

Vismodegib is a hedgehog pathway inhibitor indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

*Erivedge 150mg/day
BCNS (Gorlin Syndrome): Hereditary Defects in \emph{PTCH} Predispose to BCC

Hedgehog (Hh) Signaling Pathway Overview: Key Components of the Hh Pathway

• Key components of the Hh pathway include:
  • Hedgehog ligands (encoded by the Hedgehog gene)
  • The inhibitory receptor Patched (PTCH)
  • The signaling receptor Smoothened (SMO)

Hedgehog (Hh) Signaling Overview: Mutation-Driven Hh Signaling in BCC [Inactivating PTCH Mutations]

1. **Inactivating PTCH Mutations**
   Prevent Inhibition of SMO, Leading to Constitutive Activation of the Hedgehog Signaling Pathway

---

PTCH mutation → PTCH inhibition → SMO constitutive activation → GLI$ activation → CONSTITUTIVE SIGNAL → Transcription of target genes → Tumor cell proliferation

$GLI is a family of zinc finger transcription factors (glioma-associated oncogene)

Hedgehog (Hh) Signaling Overview: Mutation-Driven Hh Signaling in BCC [Activating SMO Mutations]

2. Activating SMO Mutations
Lead to Constitutive Activation of the Hedgehog Signaling Pathway

PTCH

SMO

CONSTITUTIVE SIGNAL

GLI

Transcription of target genes

Tumor cell proliferation

GLI is a family of zinc finger transcription factors (glioma-associated oncogene)


Vismodegib Inhibits SMO: A Mediator of Hh Pathway Signaling (Inactivating PTCH Mutation)

Vismodegib Inhibits SMO, directly blocking the Hedgehog pathway in BCCs that are driven by mutations of PTCH

NO SIGNAL

Inhibition of tumor growth

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\[ SMO \]

\[ \text{GLI}^\$ \]

\[ \text{PTCH} \]

\[ \text{NO SIGNAL} \]

\[ \text{Inhibition of tumor growth} \]


\( ^\$ \text{GLI is a family of zinc finger transcription factors (glioma-associated oncogene)} \)
My Gasparilla Pirate Buddies!