Premalignant and Malignant Non-Melanoma Skin Cancer

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Objectives

• Briefly review disease pathogenesis, presentation, and treatment options

• Discuss updates in the literature in regard to the various premalignant and malignant lesions

• Introduce ongoing research and future studies in the field of non-melanoma skin cancers
Premalignant Lesions
Actinic Keratosis

- Most common precancerous lesion
  - Can progress to SCC
    - 0.1-0.6% per lesion-year
- Treatment options:
  - Cryotherapy
  - Topical treatments:
    - 5-Fluorouracil (0.5-5%)
    - Imiquimod 5% cream
    - Ingenol mebutate
    - Diclofenac
- Photodynamic therapy
- Destructive/Surgical management
• 5-FU, imiquimod, ingenol mebutate and diclofenac are similarly efficacious but have different adverse effects and cosmetic outcomes
• Use dependent on patient preferences, prior physician and patient experience, and cost
Actinic Keratosis

Original Investigation
September 2015

Long-term Efficacy of Topical Fluorouracil Cream, 5%, for Treating Actinic Keratosis
A Randomized Clinical Trial

Hyemin Pomerantz, MD2, Daniel Hogan, MD2, David Ellers, MD1; et al

Author Affiliations

• Single course of 5% fluorouracil cream effectively reduces AK counts and need for spot treatment for longer than 2 years
• Fewer hypertrophic AKs in the treatment group at 6 months
Malignant lesions
Basal Cell Carcinoma

• Most common type of skin cancer
  – 2 million Americans affected every year
• Metastasis is extremely rare
  – 0.0028-0.55% metastatic rate
  – 50% of deaths from BCC result from direct extension into vital structure rather than metastases
Basal Cell Carcinoma

• Pathogenesis
  – Arise from pluripotent cells associated with hair follicle
  – Mutations that activate hedgehog signaling pathway → cell growth
    • Sonic hedgehog
    • Patched 1 - most common
    • Smoothened
Basal Cell Carcinoma

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Basal Cell Carcinoma

• Treatment options:
  – Surgical
    • Excision
    • Mohs Micrographic surgery (MMS)
    • Curettage and electrodessication
  – Radiation
  – Topical treatments: Imiquimod, 5-FU
  – Hedgehog pathway inhibitors (HPIs)
Basal Cell Carcinoma

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  – Hedgehog pathway inhibitors (HPIs)
    • Vismodegib (2012) and sonidegib (2015)
Basal Cell Carcinoma

• Follow up of 104 patients with locally advanced or metastatic BCC from the pivotal ERIVANCE study
• Median duration of vismodegib exposure was 12.9 months
• Increased response rates
  – Metastatic disease - 30.3% to 33.3%
  – Locally advanced – 42.9% to 47.6%
• Median duration of response improved from 7.6 – 9.5 months for locally advanced disease
• No change in side effect profile or new emerging safety signals

Original article
Pivotal ERIVANCE basal cell carcinoma (BCC) study: 12-month update of efficacy and safety of vismodegib in advanced BCC

Aleksandar Sekulic, MD\textsuperscript{a}, Michael R. Migden, MD\textsuperscript{b}, Karl Lewis, MD\textsuperscript{c}, John D. Hainsworth, MD\textsuperscript{d}, James A. Solomon, MD, PhD\textsuperscript{e,9}, Simon Yoo, MD\textsuperscript{d}, Sarah T. Arron, MD, PhD\textsuperscript{d}, Philip A. Friedlander, MD, PhD\textsuperscript{e,9}, Eileen Marmur, MD\textsuperscript{d}, Charles M. Rudin, MD, PhD\textsuperscript{d}, Anne Lynn S. Chang, MD\textsuperscript{m}, Luc Dirix, MD, PhD\textsuperscript{d}, Jeannie Hou, MD\textsuperscript{d}, Huibin Yue, PhD\textsuperscript{d}, Axel Hauschild, MD\textsuperscript{d}, on behalf of the ERIVANCE BCC Investigators
Basal Cell Carcinoma

• 8 articles (704 patients) systematically reviewed to evaluate clinical experience with hedgehog pathway inhibitors

• Vismodegib
  – Significant, consistent effect on locally advanced and metastatic BCC
  – Superior responses for metastatic BCC compared to traditional treatment

• Not enough data to review sonidegib since its approval in 2015
Basal Cell Carcinoma

• Treatment options:
  – Surgical
    • Excision
    • Mohs Micrographic surgery (MMS)
    • Curettage and electrodessication
  – Radiation
  – Topical treatments: Imiquimod, 5-FU
  – Hedgehog pathway inhibitors (HPIs)
    • Vismodegib (2012) and sonidegib (2015)
    • Itraconazole
Fig. 1. Actions of vismodegib, itraconazole and sonidegib on hedgehog pathway.
Basal Cell Carcinoma

• 29 patients enrolled in open-label study
  – Cohort A: 200mg twice daily x 1 month
  – Cohort B: 100mg twice daily x 2.5 months
• Reduced tumor size and promoted re-epithelialization in 8 patients
• None of the BCCs completely cleared
• Average tumor reduction with lower dosage (Cohort B) was comparable to higher dosage (Cohort A)
Squamous Cell Carcinoma (SCC)

• Second most common skin cancer in the United States
• 700,000 cases annually
# Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Union for International Cancer Control (UICC) 2010</th>
<th>Brigham and Women’s Hospital (BWH) 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor ≤2 cm in greatest dimension</td>
<td>0 high-risk factors*</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;2cm in greatest dimension</td>
<td>0 high-risk factors*</td>
</tr>
<tr>
<td>T2a</td>
<td></td>
<td>1 high-risk factors*</td>
</tr>
<tr>
<td>T2b</td>
<td></td>
<td>2-3 high-risk factors*</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with invasion of deep structures (muscle, cartilage, bone)</td>
<td>≥4 high-risk factors* or bony invasion</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with invasion of axial skeleton or direct perineural invasion of skull base</td>
<td></td>
</tr>
</tbody>
</table>

* BWH high-risk factors: tumor diameter ≥2cm, poorly differentiated histology, perineural invasion ≥0.1mm, tumor invasion beyond fat
Squamous Cell Carcinoma

- National comprehensive cancer network (NCCN) high-risk features:
  - Tumor location - mucosal surfaces, genitalia, periorbital, nose, lips, chin, ears, temples, sites of prior burn scars or radiation
  - Tumor diameter ≥2cm
  - Tumor depth ≥2mm (Clark level ≥IV)
  - Perineural invasion
  - Lymphovascular invasion
  - Poorly differentiated histopathology
  - Immunosuppression
    - Solid organ transplant (particularly kidney) > bone marrow transplant
Squamous Cell Carcinoma

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Squamous Cell Carcinoma

• Additional management considerations for high risk SCC:
  – Sentinel lymph node biopsy (SLNB)
    • 2015 meta-analysis recommends considering SLNB for patients with T2 lesions
  – Radiographic imaging to assess disease burden for high risk patients
    • CT, MRI, PET
  – Biomarkers for characterization of aggressive SCC
    • Matrix-metalloproteinases, p300, nuclear IKK
Squamous Cell Carcinoma

• Immunotherapy for metastatic SCC
  – Metastatic SCC has elevated expression of epidermal growth factor receptor (EGFR)
    • Cetuximab - EGFR inhibitor
    • Pantimumab - monoclonal antibody against EGFR
  – Combination therapy of cetuximab, fluorouracil, carboplatin, or cisplatin
  – PD-1 inhibitors
  – CTLA-4 inhibitor
Squamous Cell Carcinoma

- Chemoprevention
  - 2 or more NMSC + 10 or more AKs
    - Acitretin – 0.2-0.4mg/kg/day
      - 4 month up taper
      - CBC, CMP, lipids, LFTs q3mo
      - Continued indefinitely
    - Nicotinamide (niacinamide or nicotinic acid) – 500mg BID
      - 23% fewer people had NMSC
      - Lower side effect profile and no lab monitoring
Cutaneous T-Cell Lymphoma

- T cell non-Hodgkin’s lymphomas
- Average of 6 years from presentation to diagnosis
  - Clinically and histopathologically can resemble benign inflammatory disorders including psoriasis and atopic dermatitis
Cutaneous T-Cell Lymphoma

- High-throughput TCR sequencing (HTS) detected T cell clones in 46/46 CTCL patients
  - More sensitive and specific than TCRγ PCR
  - Successfully discriminated CTCL from benign inflammatory diseases
  - Demonstrated hematogenous spread of small numbers of malignant T cells in patients with new skin lesions
Cutaneous T-Cell Lymphoma

- High-throughput TCR sequencing (HTS)
  - Accurately assessed responses to therapy and facilitated diagnosis of disease recurrence
  - Diagnosed CTCL in all stages
  - Provided insights into the cell of origin and location of malignant CTCL cells in skin
Cutaneous T-Cell Lymphoma

• Largest cohort of patients with advanced MF/SS from 29 international sites
• 1,275 patients
• Identifies prognostic values to help stratify advanced-stage patients
Cutaneous T-Cell Lymphoma

- Independent poor prognostic markers for stage IV:
  - Increasing age > 60
  - Elevated LDH
  - Large cell transformation in the skin as independent poor prognostic markers
Cutaneous T-Cell Lymphoma

- Interleukin (IL-31), Th2 cytokine
  - Increased in serum of CTCL patients
- Found in IL-31 may play a role in CTCL pruritus by exerting indirect effects on sensory nerves through epidermal neoplastic T cells and keratinocytes to transmit itch
Merkel Cell Carcinoma

- Neuroendocrine carcinoma
- Linked to UV exposure and Merkel cell polyomavirus
- In the United States, the age-adjusted incidence is estimated at 0.24 per 100,000 person-years

Merkel Cell Carcinoma

Review of Treatment

- Wide local excision is the mainstay of tx (NCCN) + SLN
- Immunotherapy with PD-1/PD-L1 inhibitors is a promising treatment option for advanced or metastatic disease
- Clinical trials are currently in progress to further evaluate these novel therapeutic agents
Merkel Cell Carcinoma

- A case of metastatic MCC with a significant response to nivolumab — humanized IgG4 monoclonal PD-1 inhibitor
Merkel Cell Carcinoma

Fig. 1 Baseline and repeat FDG-PET/CT scan illustrating areas of FDG uptake. Legend: a, b and c Baseline FDG-PET/CT scan revealed hypermetabolic activity consistent with metastatic disease. d, e and f Repeat FDG-PET/CT scan following cycle 5 of nivolumab demonstrated significant decrease in size and FDG uptake of all sites of disease.
Merkel Cell Carcinoma

- 26 adults with advanced Merkel-cell carcinoma without previous systemic treatment
- Pembrolizumab, PD-1 inhibitor, dosed at 2mg/kg for 3 weeks
- Objective response rate was 56%, 4 patients had a complete response, and 10 had a partial response
Summary

• Topicals remain a viable option for chemoprevention and treatment of AKs

• Hedgehog pathway inhibitors, especially itraconazole, continue to be studies for advanced BCC

• Staging for invasive SCC continues to be utilized to help determine prognosis

• High throughput sequencing is a new diagnostic tool for CTCL

• PD-1 inhibitors may be a potential treatment option for MCC in the future
References (AKs and BCC)


References (SCC)


References (EMPD)

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• Plaza, Jose et al. HER-2/neu expression in extramammary Paget disease: A clinicopathologic and immunohistochemistry study of 47 cases with and without underlying malignancy. Journal of Cutaneous Pathology. 2009. 36(7), 729-733.

References (MPD)


References (CTCL)

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