MEDICAL THERAPY FOR BASAL CELL CARCINOMA
Conflict of Interest Disclosure

S011 - Dilemmas and Challenges in Skin Cancer Therapies and Management

I have no relevant conflicts to disclose pertaining to this presentation.

I will be discussing off-label uses of drugs.
Issues

PREVENTION

- Sunblock and sun avoidance
  - Cochrane Database Syst Rev. 2016 Jul 25;7:CD01116
- Systemic sun mitigation (Polypodium leucotomas extract)
- Systemic anti-oxidants (eg. Green tea)
  - J Nutr. 2005;135:2871
- Systemic anti-NMSC (Nicotinamide)
  - 500mg BID x 12 mo
  - BCC -20%
NCCN: BCC GUIDELINES

“The goal of primary treatment of basal cell skin cancer is the cure of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient’s preference. Customary age and size parameters may have to be modified.

“Surgical approaches often offer the most effective and efficient means of accomplishing cure, but considerations of function, cosmesis, and patient preference may lead to choosing radiation therapy as primary treatment in order to achieve optimal overall results.

“In certain indicated situations, surgical treatment may be indicated for excision of a recurrent lesion.
Basal Cell Carcinoma

- Surgery treatment of choice
- Mohs
- Excision
  - Simple
  - Tissue movement: flap, graft
- Electrodesiccation and curettage
- (Cryosurgery)

Why Medical Therapy?

- Non-invasive
- No anesthesia usually required
- Often painless
- Useful with anti-coagulation
- Useful with debilitating co-morbidity
- Larger or recurrent lesions
- Sites difficult to approach surgically
- Patients who refuse surgery
- Local skin factors: edema, atrophy
- Immediate return to normal activity
- Preservation of function; Cosmesis
“Where surgery or radiation is contraindicated or impractical, topical therapies may be considered, even though the cure rate may be lower.”
Medical Therapies: BCC

- **Topical therapy**
  - 5-FU
  - Imiquimod
  - Ingenol mebutate
  - Cryotherapy

- **Intra-lesional Therapy**
  - 5FU
  - Interferon

- **Systemic therapy**
  - Hedgehog pathway inhibitors (Vismodegib, Sonidegib)

- **Photodynamic therapy**

- **Radiotherapy**
  - Superficial radiation
  - Brachytherapy: HDR, LDR, Electronic
Medical Therapies: BCC

- **Topical therapy**

- **Intra-lesional Therapy**

- **Systemic therapy**
  - **Photodynamic therapy** Photodermatol Photoimmunol Photomed. 2015;31:44-53

- **Radiotherapy**
nBCC: Imiquimod Comparative Dosing

- Multi-national, open label, dose-response study
- Imiquimod 5%
- 6 weeks: QD x 3d/wk, QD x 7d/wk, BID x 3d/wk, BID x 7d/wk
- 12 weeks: QD 3d or 5d or 7d/wk, BID x 7d/wk
- Tumor excised 6 weeks after Rx finalized
- HIGHEST clinical/histologic cure: QD x 7d/wk, 6 or 12 weeks; cure rates were: 71% (6wk Rx) and 76% (12wkRx)
- Unacceptably low cure rate to use as monoRx

Arch Dermatol 2002;138:1165-71
sBCC: Comparative Efficacy

- RCT, single-blind, non-inferiority Dutch; n = 601
- MAL-PDT (x 2 sessions), 5% 5-FU (BID x 4wk), 5% Imiquimod (5x/wk x 6 wks)

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>No Disease: 3 mo AND 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiquimod 5%</td>
<td>83.4%</td>
</tr>
<tr>
<td>5-FU</td>
<td>80.1%</td>
</tr>
<tr>
<td>MAL-PDT</td>
<td>72.8%</td>
</tr>
</tbody>
</table>

Lancet Oncol 2013;14:647-54
Imiquimod for BCC: 5 Year Study v Surgery

- Five year prospective study
- Imiquimod 5% (QD x 6 wk superficial or 12 wk nodular)
- Compared to excisional therapy with 4mm margin
- Enrolled: 501; Analyzed at 3 years: 401 at 5 years: 383

<table>
<thead>
<tr>
<th>Cure rate at....</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial BCC, Surgery</td>
<td>98.0</td>
<td>96.8</td>
</tr>
<tr>
<td>Superficial BCC, Imiquimod</td>
<td>85.1</td>
<td>83.8</td>
</tr>
<tr>
<td>Nodular BCC, Surgery</td>
<td>98.9</td>
<td>98.8</td>
</tr>
<tr>
<td>Nodular BCC, Imiquimod</td>
<td>81.8</td>
<td>81.1</td>
</tr>
</tbody>
</table>

*Lancet Oncol. 2014;15:96-105*
Imiquimod and Nodular BCC: Adjunctive role

- **Imiquimod PLUS…..**
- **Mohs: Pre-surgery to shrink tumor prior to surgery**
- **Mohs: Post-surgery w/ clear margins not obtainable**
- **Curettage: Instead of desiccation for cosmesis**
- **Curettage and desiccation: Improved cosmesis?**

*J Drugs Dermatol 2006;5:461*
*J Drugs Dermatol 2008;7(S):s7*
*Dermatol Surg 2004;30:1462*
## Imiquimod One Week After Curettage: nBCC

<table>
<thead>
<tr>
<th>Number of lesions</th>
<th>How imiquimod used</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, Nodular (Cured)</td>
<td>3.75% QD x 4 weeks</td>
<td>J Clin in Aesthet Dermatol.2011 ;4:39-43</td>
</tr>
<tr>
<td>57, Nodular + Superficial (100% cure)</td>
<td>5% 5x weekly x 6 weeks</td>
<td>J Drugs Dermatol. 2008;7(1 Suppl 1):s15-6</td>
</tr>
<tr>
<td>101, Nodular (96% cure)</td>
<td>5% 5x weekly x 6 weeks</td>
<td>J Drugs Dermatol. 2008;7(1 Suppl 1):s7-14</td>
</tr>
<tr>
<td>17, Nodular (100% cure)</td>
<td>5% 5x weekly x 6 weeks</td>
<td>J Drugs Dermatol. 2007;6:910-14</td>
</tr>
<tr>
<td>34, Nodular (94% cure)</td>
<td>5% 7x weekly x 6-10 weeks</td>
<td>Australas J Dermatol. 2006;47:46-8</td>
</tr>
</tbody>
</table>
Ingenol mebutate for Basal Cell Carcinoma

- Prior Australian clinical trials, differing dosage schedules
  - Phase IIa, n= 60, sBCC, treated either two consecutive days or days 1 and 8; concentrations 0.0025%, 0.01% or 0.05%
  - Best result (63%) in .05% x 2 consecutive days
    - Australas J Dermatol 2010;51,99–105
- Phase I/II, n = 36, sBCC and nBCC treated three consecutive days with concentrations of .01-.03%
- Best result (78%) in sBCC, but there were recurrences at 15 mo of followup
Ingenol mebutate for Basal Cell Carcinoma

- sBCC, forehead (Korea)
  - .015% QD x 4: Resolved at 10 weeks
  - 3 mo f/u
- 9 sBCC in seven patients (USA)
  - .05% QD from 2-7 days, as tolerated: Resolved 2-4 weeks
  - Variable follow, up to 14 mo
- 20 sBCC in twenty patients (Italy)
  - .05% QD x 2: All resolved in 8 weeks
  - 6 mo f/u
    - *Dermatol Ther. 2016;29:470-472*
Cryotherapy: New Concept

- **Intra-lesional cryosurgery**
- Cryoprobe inserted normal skin
- Advanced ~2-3mm beneath tumor
- Exits out of contralateral normal skin
- Attached to LN$_2$ canister
- LN$_2$ flows until ice ball forms, with 10mm margin
- Probe thaws, removed, wound care
- **Risks:** dyspigmentation, slow healing, pain
- Single session is curative

J Dermatolog Treat, 2015; 26: 147–150*
Intra-lesional Cryotherapy

Intra-lesional 5-fluorouracil (FU) as a treatment for nonmelanoma skin cancer (NMSC): A review

Lauren Metterle, BS, Christopher Nelson, MD, and Nishit Patel, MD
Tampa, Florida

The treatment paradigm for nonmelanoma skin cancer remains surgical. This fact combined with its remarkably high incidence positions it as the fifth most costly cancer to treat in the Medicare population. To address this, consideration of alternative medical therapeutics is warranted. Intralesional 5-fluorouracil is a potentially affordable option that may demand further investigation. This literature review examines current data on its efficacy and adverse effects. (J Am Acad Dermatol 2016;74:552-7.)

Key words: basal cell carcinoma; 5-fluorouracil; intralesional; management; medical therapy; non-melanoma skin cancer; squamous cell carcinoma.
Intra-lesional 5-FU Injection for BCC

**Reviews**

Intralgesional 5-fluorouracil (FU) as a treatment for nonmelanoma skin cancer (NMSC): A review

BCC incidence makes it the 5th costliest tumor Medicare population
Primary procedure fees constitute majority of expense
Including closure fees and surgical pathology: Average $788/lesion
COST 50mg/ml, 50ml vial of 5-FU = $12-26
Two year unopened shelf life; 72 hours after opened
No standardization: QOW, QW, BIW have been used
4-6 injections to clear

*J Am Acad Dermatol. 2016;74:552-7*
Intra-lesional 5-FU Injection for BCC

Treatment of Cutaneous Neoplasms by Intralesional Injections of 5-Fluorouracil (5-FU)

BAYLOR KURTIS, M.D., AND THEODORE ROSEN, M.D.

Successful management of keratoacanthomas and basal-cell epitheliomas by intralesional injections of 5-fluorouracil is reported.

5-FU has been used effectively by topical application in the management of some benign, premalignant, and malignant cutaneous neoplasms. Intralesional injection of the agent has recently been reported to be therapeutically effective in nodular basal-cell epitheliomas and keratoacanthomas. We herewith report our experience and generally favorable results in the use of 5-FU by intralesional deposition in the latter conditions.

MATERIALS AND METHODS

Three keratoacanthomas and three basal-cell epitheliomas were treated. Clinical diagnoses were confirmed by biopsies. The six lesions were injected with 5-FU in its commercially available form for systemic chemotherapy (50 mg/cc) after infiltration with a
What About The Disasters?

- Large, neglected lesions
- Multiply recurrent
  - Despite surgery (including Mohs)
  - Despite adequate/appropriate radiotherapy
  - Despite both surgery and radiation
- Poor patient protoplasm
- Gorlin Syndrome
- Metastatic BCC (rare)
Hedgehog Pathway Inhibitors

- Directly suppress SMO which is upregulated due to mutation in its suppressor (PTCH)
- **Currently approved: vismodegib and sonidegib**
  - Vismo: 150mg/day and Soni: 200mg/day
- Same AE profile, which is accompanied by high dropout rate in studies and in real life
- Muscle cramps, alopecia, taste abnormalities, weight loss, fatigue, nausea, diarrhea, and decreased appetite
- Soni, maybe Vismo: Monitor CPK (rhabdomyolysis)
- Embryotoxic and teratogenic
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REVIEW

For reprint orders, please contact: reprints@futuremedicine.com

Managing adverse events associated with vismodegib in the treatment of basal cell carcinoma

Kate Fife*, Robert Herd‡, Susan Lalondrelle§, Ruth Plummer¶, Amy Strong†, Sarah Jones∥ & John T Lear∥∥
<table>
<thead>
<tr>
<th>AE</th>
<th>Symptoms</th>
<th>Time to onset in clinical trials (months)</th>
<th>Severity</th>
<th>Management strategies (in order of priority)</th>
<th>AE resolution upon stopping vismodegib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste disturbance</td>
<td>Loss of taste&lt;br&gt;Sour to sweet&lt;br&gt;Sweet to sour&lt;br&gt;Metallic taste&lt;br&gt;Change of taste of alcohol&lt;br&gt;Food tasting bland&lt;br&gt;Sensitivity to spicy foods</td>
<td>1.4–6.5</td>
<td>Mild/moderate</td>
<td>Managing expectations&lt;br&gt;Food swaps to identify food that is pleasant in the context of taste changes&lt;br&gt;Dietetic referral&lt;br&gt;Monitoring blood to check for raised creatinine levels&lt;br&gt;Treatment breaks (&gt;4 weeks may be needed)</td>
<td>Yes (2–6 months after stopping vismodegib)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>Cramps in hands/feet&lt;br&gt;Cramps in abdomen&lt;br&gt;Often experienced after physical activities</td>
<td>1.3–2.8</td>
<td>Mild/moderate</td>
<td>Quinine (200 mg)&lt;br&gt;Treatment breaks (4–8 weeks)&lt;br&gt;Gentle exercise of affected areas&lt;br&gt; Muscle relaxants (e.g., baclofen 15–30 mg daily; temazepam 10–20 mg daily)</td>
<td>Yes (1 month after stopping vismodegib)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Can be patchy or cover the whole head&lt;br&gt;Includes body hair</td>
<td>3.4–5.5</td>
<td>Mild/moderate</td>
<td>Managing expectations&lt;br&gt;Wig referral</td>
<td>Yes (usually 6–12 months, occasionally longer)</td>
</tr>
</tbody>
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AE: Adverse event.
Hepatotoxicity with Vismodegib: An MD Anderson Cancer Center and Research on Adverse Drug Events and Reports Project

Hepatotoxicity signal
Two severe liver toxicity cases
94 addt’l reports, 35 serious
Predicting Hedgehog Pathway Inhibitor Resistance???
## Hedgehog Pathway Inhibitors: Vismodegib

<table>
<thead>
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<th>Parameter</th>
<th>Initial Evaluation (12 Months)</th>
<th>Follow-up (+18 Months)</th>
<th>Follow-up (+24 Months)</th>
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<tr>
<td>Objective response rate</td>
<td>43%</td>
<td>47.6%</td>
<td>60.3%</td>
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<tr>
<td>Complete response</td>
<td>21%</td>
<td>22.2%</td>
<td>31.7%</td>
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<tr>
<td>Partial response</td>
<td>22%</td>
<td>25.4%</td>
<td>28.6%</td>
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<td>Stable Disease</td>
<td>38.1%</td>
<td>34.9%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Median progression-free survival</td>
<td>9.5 months</td>
<td>9.5 months</td>
<td>12.9 months</td>
</tr>
<tr>
<td>Adverse events: discontinuation</td>
<td>12%</td>
<td>Not reported</td>
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Hedgehog Pathway Inhibitors: Vismodegib

Cochrane-type systematic analysis
Included pivotal study plus other published trials & case series
Total trials = 8 and Total patients clinically evaluable = 704
Objective response IaBCC weighted average 64.7%
Complete response weighted average 31.1%
AE-related discontinuation of therapy average 28.2%

“This analysis supports the opinion that vismodegib may be more useful as a means to control laBCC than to provide a definitive cure.”

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Complete response weighted average 31.1%
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Intermittent Dosing: Reduce AEs, Retain Rx Effect?

N = 7 (1 Gorlin Syn)
1 Week on
1-3 Weeks off


N = 2, Both Gorlin Syn
1-2 Months on
2 Months off

JAMA Dermatol. 2016 Feb;152(2):223-4
Two intermittent vismodegib dosing regimens in patients with multiple basal-cell carcinomas (MIKIE): a randomised, regimen-controlled, double-blind, phase 2 trial

Prof Brigitte Dréno, MD, Prof Rainer Kunstfeld, MD, Prof Axel Hauschild, MD, Prof Scott Fosko, MD, David Zloty, MD, Bruno Labeille, MD, Prof Jean-Jacques Grob, MD, Susana Puig, MD, Frank Gilberg, PhD, Daniel Bergström, PhD, Damian R Page, PhD, Gary Rogers, MD, Prof Dirk Schadendorf, MD

Published: 07 February 2017
Vismodegib: Intermittent Dosing Trial

- 229 adult patients, mostly immunocompetent and good overall functional status; 37% Gorlin Synd.
- Assigned to two treatment groups for 72 wk trial
  - QD Induction x 3 mo, then 2mo off, 3 mo on x 3 cycles
  - QD induction x 6 mo, then 2mo off, 2 mo on x 3 cycles
- BOTH treatment regimens were effective
  - 54-62.7% reduction from baseline in number BCC
  - 57-76% had at least 50% reduction in number BCC
  - 64-72% experienced NO new BCC by EOT
- Adverse events were still common; 23% Dropout rate

Lancet Oncol 2017; Feb 7
http://dx.doi.org/10.1016/S1470-2045(17)30072-4
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Arm A, n (%)</th>
<th>Treatment Arm B, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>113 (99.1)</td>
<td>110 (97.3)</td>
<td>223 (98.2)</td>
</tr>
<tr>
<td>Muscle spasm</td>
<td>83 (72.8)</td>
<td>93 (82.3)</td>
<td>176 (77.5)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>75 (65.8)</td>
<td>75 (66.4)</td>
<td>150 (66.1)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>72 (63.2)</td>
<td>73 (64.6)</td>
<td>145 (63.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (21.1)</td>
<td>26 (23.0)</td>
<td>50 (22.0)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>24 (21.1)</td>
<td>21 (18.6)</td>
<td>45 (19.8)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21 (18.4)</td>
<td>17 (15.0)</td>
<td>38 (16.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (17.5)</td>
<td>18 (15.9)</td>
<td>38 (16.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>23 (20.2)</td>
<td>14 (12.4)</td>
<td>37 (16.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15 (13.2)</td>
<td>20 (17.7)</td>
<td>35 (15.4)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>18 (15.8)</td>
<td>16 (14.2)</td>
<td>34 (15.0)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>18 (15.8)</td>
<td>12 (10.6)</td>
<td>30 (13.2)</td>
</tr>
<tr>
<td>Ageusia</td>
<td>14 (12.3)</td>
<td>13 (11.5)</td>
<td>27 (11.9)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase increase</td>
<td>11 (9.6)</td>
<td>15 (13.3)</td>
<td>26 (11.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (9.6)</td>
<td>12 (10.6)</td>
<td>23 (10.1)</td>
</tr>
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</table>
Hedgehog Pathway Inhibitors: Sonidegib

<table>
<thead>
<tr>
<th>Parameter</th>
<th>12-month Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg* (n = 66)</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>57.6%</td>
</tr>
<tr>
<td>Complete response</td>
<td>4.5%</td>
</tr>
<tr>
<td>Partial response</td>
<td>53.0%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>33.3%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1.5%</td>
</tr>
<tr>
<td>Median response duration</td>
<td>Not reached</td>
</tr>
<tr>
<td>Discontinued due to adverse</td>
<td>27.8%</td>
</tr>
<tr>
<td>events</td>
<td></td>
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</tbody>
</table>
Traditional Hedgehog Pathway Inhibitors
What We Do Not Know!

- How long to treat? What is the end point?
- What to do about resistance?
  - Can we predict it?
  - Can we prevent it?
- Use as surgical adjuvant?
- Use as radiotherapy adjuvant?
- Combination with other HHIs?
- Optimum intermittent dosing regimen?
- How to minimize or treat side-effects?
- Increased risk of new SCCA?
Other Hedgehog Pathway Inhibitors

- Arsenic trioxide
- Imiquimod
- Itraconazole

References:
JAMA Dermatol 2016;152:452-56
J Clin Oncol 2014;32:745-51
Cancer Cell 2013;23:23-34
Radiotherapy

- Utility of radiotherapy: PRIMARY or SECONDARY
- Patients with debilitating co-morbidities
- Patients on anti-coagulants
- Aging patients
- Patients who refuse surgery
- Larger or recurrent lesions
- Sites difficult to approach surgically
- Sites of cosmetic concern: nasal ala, eyelid
- Local cutaneous factors: edema, atrophy, MRSA
- Palliative therapy
Treatment of BCC: Surgical vs. Medical

AVAILABLE / EMERGING

STANDARD