Non-Surgical Options for Non-Melanoma Skin Cancer

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Disclosure
Genentech, DUSA, Celgene

Objectives
• 1. Discuss 5 Non-surgical Treatment options for Skin Cancers
• 2. Review the Pros and Cons of Non-surgical Skin Cancer Treatments
• 3. Select Situations and Cases in which these treatments might be helpful to your patients

Outline
• 1. Intrallesional Chemotherapy
• 2. Photodynamic Therapy
• 3. Imiquimod Immunotherapy
• 4. Systemic Retinoids and Cetuximab
• 5. Brachytherapy
• 6. Vismodegib and Sonidegib

Case: BCC at Eyelid

Non-Surgical Cases
Skin Cancer Risk Reduction

- Sunscreen
- Caffeine
- Nicotinamide

Skin Cancer Risk Reduction: Caffeine

The Skin Cancer Foundation's Response to Study on Daily Coffee Consumption and Melanoma Risk

New York, NY—January 1, 2019—A recent study published in the Journal of the National Cancer Institute found that daily coffee consumption may protect against malignant melanoma. Researchers analyzed data from 447,287 non-Hispanic white individuals aged 50-71 years from three prospective cohort studies to evaluate the association between coffee consumption and risk of melanoma. They observed that daily coffee consumption was associated with a reduced risk of melanoma. The study concluded that daily coffee consumption may be protective against melanoma and suggested that further research is needed to confirm these findings.

Skin Cancer Risk Reduction: Nicotinamide

A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

Researchers conducted a Phase 3 randomized trial to evaluate the efficacy of nicotinamide for chemoprevention of skin cancers. The study enrolled 1,000 participants with actinic keratoses and randomized them to receive either 5% nicotinamide cream or a placebo cream. The primary endpoint was the rate of new nonmelanoma skin cancers at 12 months. The results showed a significant reduction in new nonmelanoma skin cancers in the nicotinamide group compared to the placebo group. The study concluded that nicotinamide is a promising chemopreventive agent for actinic keratoses.

Skin Cancer Risk Reduction: Nicotinamide

Intralesional Chemotherapy

At 12 months, the rate of new nonmelanoma skin cancers was lower by 23% (95% confidence interval [CI], 4 to 18) in the nicotinamide group than in the placebo group ($P=0.002$). Similar differences were found between the nicotinamide group and the placebo group with respect to new basal-cell carcinomas (20% [95% CI, 6 to 31]) lower rate with nicotinamide; $P=0.12$). The number of actinic keratoses was 11% lower in the nicotinamide group than in the placebo group at 3 months ($P=0.01$), 14% lower at 6 months ($P=0.001$), 20% lower at 9 months ($P=0.001$), and 33% lower at 12 months ($P=0.001$). No noteworthy between-group differences were found with respect to the number or types of adverse events during the 12-month intervention period, and there was no evidence of benefit after nicotinamide was discontinued.
Recurrent Keratoacanthoma/SCC

Intralesional Chemotherapy

Intralesional Chemotherapy for Nonmelanoma Skin Cancer: A Practical Review

- Methotrexate, Bleomycin, Interferon, 5-Fluouracil
- 9 Articles on 82 Keratoacanthomas (23 BCCs)
- 98.5% were cured!

5-Fluoracil:
- 50 mg/ml 5-FU
- 0.5 to 1.0 cc for each treatment (3.0 ccs total)
- 3 to 8 treatments, weekly

Keratoacanthoma/SCC: Intralesional 5-FU

Eruptive Keratoacanthomas/SCCs

Intralesional 5-FU for Multiple Eruptive Keratoacanthomas
Intralesional 5-FU for Multiple Eruptive Keratoacanthomas

Keratoacanthoma/SCC

Intralesional Chemotherapy

Intralesional Chemotherapy

Intralesional Chemotherapy

Case 1: IL-5FU
**Cost and Reimbursement of IL-5FU**

**Photodynamic Therapy**

- Temperature
- Timing
- Light source
- Absorption Measurement
- Diagnostic Use
- Other Indications

**Actinic Keratosis**

**High variability in PpIX production among patients**

Patients enrolled: 82
Patients with usable spectra: 64
Lesions on head/face: 44 (67%)

Large subpopulation Presenting low PpIX

67% < FL mean
Photodynamic Therapy and Diagnosis

Some patients show high PpIX production

Patient ID: 76
Follow up call
Time: 96 hrs post TX
Pain: 8
Discomfort: lasted ~72 hrs
Oral meds: Patient used Tylenol and Benadryl
Described treated site as: 'terrible sunburn'
Peeling: Mild peeling reported at 4 days

Some patients show very low PpIX production

Patient ID: 66
Follow up call
Time: 48 hrs post TX
Pain: 1
Discomfort: lasted ~24 hrs
Oral meds: Patient used Tylenol
Described treated site as: 'blotchy sunburn'
Peeling: None reported

PDT for Actinic Cheilitis

• 3 patients: 100% clear
  - 1 patient 100% clear after 1 treatment
• 13 patients: 75% improved
• 2 patients: 50% improved
• 1 patient: 25% improved
• 16/19 patients were > or = 75% improvement
• Correlated with patient assessment
  • 84%

From: Methyl-ALA–Induced Fluorescence in Photodynamic Diagnosis of Basal Cell Carcinoma Prior to Mohs Micrographic Surgery

Figure Legend:

PDT for Actinic Cheilitis

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  - 1 patient 100% clear after 1 treatment
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  • 84%
Case #001

PDT for Actinic Cheilitis

• 1.5 hour incubation
• 16:40 minute activation (BLU-Light)
• > 80% of patient will improve (>75%)
• Minimal adverse events
• Include in PDT AK treatment

PDT Pearls

• Stable Temperature in room
• No cooling (Fan is OK)
• 1 hour incubation not always effective
• Better to take breaks (1-2 minutes, restart)
• Significant Variation in PPIX absorption
• Correlation with erythema / pain and effect
• Red Light (~630 nm) and Blue Light (~415 nm)

Future PDT

• Blue Light (~415 nm) and Red Light (~630 nm)
• Device to assess absorption and dosing
• Multiple indications
• Daylight PDT
• Alternative dosing schedules
• Diagnostic Tool for tumor margins
• Actinic Cheilitis

Imiquimod Immunotherapy

Basal Cell Carcinoma: Nodular

- NODULAR BCC
- CONTROLLED & BLINDED
- 6 WEEKS/12 WEEKS
- 98/90 PATIENTS
- POST-TREATMENT EXCISION
- 6 WEEKS/DAILY: 71% CLEARANCE
- 12 WEEKS/DAILY: 76% CLEARANCE

• EFFICACY OF TOPICAL IMIQUIMOD 5% CREAM FOR THE TREATMENT OF NODULAR BASAL CELL CARCINOMA: COMPARISON OF DOSING REGIMENS
ARCHIVES OF DERMATOLOGY 2002;138:1165-71 USA AUSTRALIA NEW ZEALAND

Post-Treatment Excision

99/92 PATIENTS
Basal Cell Carcinoma (Nodular)

Melanoma in-situ

Melanoma in-situ (Residual)

Recurrent Melanoma In-situ
AT FOREHEAD FLAP on NASAL TIP

METASTATIC MELANOMA
TREATMENT OF LOCALLY RECURRENT MUCOSAL MELANOMA WITH TOPICAL IMIQUIMOD

- 3 CASE REPORTS
- RECURRENT MUCOSAL MELANOMA
- POST EXCISION
- RESPONDING TO IMIQUIMOD

IMIQUIMOD FOR THE TREATMENT OF MELANOMA IN-SITU RECOMMENDATIONS

- SURGICAL EXCISION IS GOLD STANDARD!
- IMIQUIMOD 5% CREAM IS AN OPTION
- 55% to 90% CLEARANCE RATE (SMALL STUDIES)
- PRE-TREAT with TAZAROTENE FOR 2 WEEKS
- 5 TIMES WEEKLY FOR 12 WEEKS
- HOLIDAY OR REST PERIODS EXPECTED
- 25% INFECTIONS/Colonization (Staphylococcus aureus)
- POST-TREATMENT BIOPSY (4 WEEKS FROM LAST DOSE)
- WOOD’S LAMP EXAM & FOLLOW-UP FOR LIFE
Systemic Skin Cancer Treatment: Retinoids and Cetuximab

Retinoids for Cancer

- Acute promyelocytic leukemia
- Hairy cell leukemia
- Ovarian cancer
- Breast cancer
- Colon cancer
- Squamous cell carcinoma

CUTANEOUS SQUAMOUS CELL CARCINOMA IN ORGAN TRANSPLANT RECIPIENTS

- 179 PATIENTS WITH 475 SCC
- 100-FOOLD INCREASE IN SCC
- MEN: HEAD & NECK (EAR)
- WOMEN: TRUNK
- YOUNG: CHEST
- OLD: FACE
- SUN EXPOSURE WAS MOST IMPORTANT FACTOR EXPLAINING THE DIFFERENCES

LOW-DOSE RETINOIDS IN THE PREVENTION OF CUTANEOUS SQUAMOUS CELL CARCINOMAS IN ORGAN TRANSPLANT RECIPIENTS

- RETROSPECTIVE
- 32 PATIENTS WITH AT LEAST 1 SCC
- RETINOID GIVEN AT 0.2-0.4 mg/kg DAY FOR 12 MONTHS
- 28 PATIENTS CONTINUALLY TREATED
- 2.9 SCC/YEAR PRETREATMENT
- MEAN DIFFERENCE
  - YEAR 1: 1.46
  - YEAR 2: 2.20
  - YEAR 3: 2.14
Oral Retinoids and Interferon

• Epidermal Growth Factor Inhibitor
• Chimeric monoclonal antibody
• Colorectal and Head and Neck Cancer
• SCC of Head and Neck Cancer, with Platinum
• Combination with Radiation

High-Risk Cutaneous Squamous Cell Carcinoma

• Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin.
• Cetuximab in refractory skin cancer treatment.
• An evolving paradigm for the workup and management of high-risk cutaneous cell carcinoma.
• COMBINATION therapy with radiation, paclitaxel, etc.

Cetuximab

Cetuximab

Cetuximab

Cetuximab
**Brachytherapy**

**Brachytherapy for Non-Melanoma Skin Cancer**

**Xoft Skin eBx**

Electronic Brachytherapy for the Treatment of Non-Melanoma Skin Cancer

**Skin eBx**

- Effective, convenient, non-surgical treatment option for select NMSC patients (BCC & SCC)
- Not a replacement for Mohs surgery
- Utilizes a miniature, non-isotopic 50 kV X-ray source
- Minimal shielding
- 8 treatments over 4 weeks, <5 minutes each
- Precise targeting of the tumor site using an applicator ranging in diameter 10mm to 50mm
- No pain or discomfort
  - Patient can resume normal activities immediately

**Clinical Outcomes and Patient Reported Outcomes Following Electronic Brachytherapy for the Treatment of Non-Melanoma Skin Cancer**

- Study enrollment: 187 subjects, 282 lesions
- Mean follow-up: 12.5 months
- Good-to-excellent cosmesis at up to 5 years f/u
- Excellent local control (98.7%) at up to 5 years f/u
- 96 percent of NMSC patients surveyed between 32 to 72 months post-treatment with Xoft eBx were satisfied with their clinical and cosmetic treatment outcomes.
- HDR electronic brachytherapy provides a convenient, effective, nonsurgical treatment option for eligible NMSC patients.
  - Ideal patients include those who are older (>60) or with significant medical comorbidities and/or with lesions in cosmetically sensitive locations

**Squamous cell carcinoma on right cheek treated with 40Gy to a 5mm depth**

- Pre-treatment
- Fraction 1
- Fraction 2
- Fraction 3
- 6 months post-treatment
- 1 year post-treatment
- 2 years post-treatment
- 3 years post-treatment
Vismodegib and Sonedegib

Basal Cell Carcinoma: Advanced and Metastatic (Complex)

Advanced, Metastatic, Complex BCC

Vismodegib and Sonidegib

• Hedgehog Pathway Inhibitors

Vismodegib:
• Oral 150 mg daily
• Metastatic & Advanced BCC
• Higher Efficacy than Data Suggests
• Manageable Side Effects!
• Drug Holidays
• Tolerated by most patients!
• Patient Motivation
• Dermatology Drug!

Efficacy and Safety of Vismodegib

Vismodegib: Good, Bad and Unknown

• Side Effects:
  — Muscle Cramps/Spasms
  — Nausea and Vomiting
  — Diarrhea
  — Weight Loss
  — Hair Loss (recoverable)
  — Dysgeusia (recoverable)

• How to use it: ???
  — Not a cure in all patients!
  — Tumor Shrinkage!
  — Surgical Adjuvant?
  — Use in BCC Nevus Syndrome?
  — How long to treat? End Point?
  — Intermittent Therapy?

• Higher Efficacy than Data Suggests
• Manageable Side Effects!
• Drug Holidays
• Tolerated by most patients!
• Patient Motivation
• Dermatology Drug!
Vismodegib Case #1

Vismodegib Case #2
Basal Cell Carcinoma Nevus Syndrome

Vismodegib #3

Vismodegib Case #3

Vismodegib Case #3

Vismodegib Case #4
Vismodegib Case #5

Vismodegib Case #6

Vismodegib: Future Use

1. Intermittent Dosing: 2 months on/1 month off
2. VisMOHS: Tumor shrinkage then clearance with Mohs
3. Use in BCC Nevus Syndrome Patients

Case: BCC at Eyelid

Summary

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2. Photodynamic Therapy
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4. Systemic Retinoids and Cetuximab
5. Brachytherapy
6. Vismodegib and Sonidegib