Lasers Treatment of Basal Cell Carcinoma: Incorporating into your clinical practice

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Disclosures

- Alastin – Paid consultant
- Allergan – Stockholder, Scientific advisory board, speaker's bureau
- BTL – Equipment
- Cutera – Paid consultant
- Dermaflash – Paid spokesman
- Inmode – Honorarium, Scientific Advisory Board, Speaker's bureau, equipment
- Merz – Data safety monitoring board, Scientific Advisory Board
- Revance – Primary Investigator
- Rodan + Fields – Scientific Advisory board
- Sciton – Scientific Advisory board, Equipment
- Sienna Biopharmaceuticals – Scientific Advisory board, Primary Investigator

Background

• Basal cell carcinoma (BCC) is the most common skin cancer
• Surgical options frequently result in disfigurement
• Topical therapies often result in recurrence
• Need for alternative, non-surgical options
• Effective, efficient, low risk of side effects
• This has led to the emergence of laser and light-based therapeutic options

Mechanism of Action

• Based on selective photothermolysis of tumor vasculature
• Prototypic feature is presence of telangiectatic vessels
• Microvasculature of BCC are of significantly larger caliber than normal skin and more fragile
  - 40 μm vs 15 μm
  - Taller pulse duration to size of vessels
• Targeting microvasculature -> tumor regression
• Spare surrounding normal tissue

What is the ideal wavelength?

- 595 nm PDL is well absorbed by oxyhemoglobin
- 1064 nm Nd:YAG penetrates to deep arterial vessels

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Trial</th>
<th># of Subjects/Tumors</th>
<th>Number of Treatments/Interval</th>
<th>Laser Settings</th>
<th>Evaluation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allison et al. (2003)</td>
<td>Prospective, open-label</td>
<td>7 pts/1</td>
<td>1</td>
<td>585 nm, 0.45 ms, 6.0 J/cm²</td>
<td>Excision 12 weeks after laser tx</td>
<td>1/7 showed clearance</td>
</tr>
<tr>
<td>Campolmi et al. (2008)</td>
<td>Prospective, open-label</td>
<td>20 pts/5</td>
<td>Q20 days</td>
<td>595 nm, 7.5 J/cm², 7 mm spot, 1.5 ms, or 6.5 J/cm², 0.5 ms</td>
<td>Clinical/12 to 24 months</td>
<td>16/20 had a complete response. (3 recurrences and 1 did not respond)</td>
</tr>
<tr>
<td>Shah et al. (2009)</td>
<td>Matched historical control</td>
<td>12 pts/20 BCC</td>
<td>Q2 weeks</td>
<td>595nm, One pass, 15 J/cm², 3 ms, no cooling, 7 mm spot, 10% overlap</td>
<td>Excision 2 weeks after last laser tx</td>
<td>91.7% (11/12) BCCs &lt;1.5cm showed complete response, 25% (n.2/8) BCCs ≥1.5cm showed complete response</td>
</tr>
<tr>
<td>Konnikov et al (2011)</td>
<td>Open-label</td>
<td>14 pts/20 BCC</td>
<td>Q3-4 weeks</td>
<td>595nm, One pass, 15 J/cm², 3ms, DCD 30/20, 7 mm spot, 10% overlap</td>
<td>Biopsy or Excision at 1 year +</td>
<td>90% (18/20) BCCs showed no evidence of BCC more than 12 months after PDL treatment.</td>
</tr>
<tr>
<td>Ballard et al. (2011)</td>
<td>Open-label</td>
<td>7 pts/9 BCC</td>
<td>1</td>
<td>585 nm, 0.45 ms, 7 mm spot, and 9.0 J/cm², no cooling, 10% overlap</td>
<td>Deep shave 4 weeks after laser tx</td>
<td>55.6% (5/9) sites demonstrated no evidence; 44% (4/9) sites showed residual BCC.</td>
</tr>
<tr>
<td>Tran et al. (2012)</td>
<td>Randomized-controlled</td>
<td>20 pts/21 BCC (2 SCC)</td>
<td>1</td>
<td>S1 group: 595 nm, 15 J/cm², 3 ms, no cooling, 7 mm spot, 10% overlap, two passes. S2 group: 595 nm, 7.5 J/cm², 3 ms, no cooling, 10 mm spot, 10% overlap, double stacked pulses</td>
<td>Excision</td>
<td>25% (2/8) clearance in S1 group, 71% (5/7) clearance rate in S2 group</td>
</tr>
</tbody>
</table>

PDL

- Well absorbed by oxyhemoglobin.
- Depth of penetration is limited into the superficial dermis.
- Increase risk of subdermal recurrence.

**Author Type of Trial**

<table>
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<th># of Subjects/Tumors</th>
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<tbody>
<tr>
<td>Ibrahimi et al.</td>
<td>(2011)</td>
<td>Case Report</td>
<td>1 pt/18 BCC</td>
<td>1 755nm, 2 passes, 100 J/cm², 3 ms, no cooling, 8mm spot, 10% overlap</td>
<td>Clinical/1 biopsy at 7 months</td>
<td>83% (15/18) clinical response. One lesion examined had histopathologic clearance.</td>
</tr>
<tr>
<td>Jalian et al.</td>
<td>(2014)</td>
<td>Open-label</td>
<td>10 pts/13 BCC</td>
<td>4 Q2-4 weeks 585nm, 7mm spot, 8 J/cm², 2 ms, 250 ms delay; 1,064nm, 40 J/cm², 15 ms, single pass, 10% overlap, forced chilled air</td>
<td>Excision 2-4 weeks after last laser tx</td>
<td>58% (7/12) clearance. 75% (6/8) BCCs &lt;1 cm showed complete response.</td>
</tr>
<tr>
<td>El-Tonsy et al.</td>
<td>(2004)</td>
<td>Open-label</td>
<td>37 pts</td>
<td>Continuous-wave 1064 nm Nd:Yag laser, 10 W, 8mm spot, and irradiation time up to 1 minute</td>
<td>Biopsy/3 months after clinical resolution</td>
<td>97.3% (36/37) were completely cured. 1 recurrence (2.7%).</td>
</tr>
<tr>
<td>Moskalik et al.</td>
<td>(2009)</td>
<td>Retrospective</td>
<td>3346 BCC</td>
<td>1 or 2 1060 nm, 1–4.5 ms, 700 J and 0.5 cm spot or 1000 J and 1.5 cm. Nd:YAG also used in pulsed mode, 1060/1320 nm, 1 ms, 0.6 J, 1 mm spot. Nd laser: 1–5 pulses at 45- to 60-sec intervals, total dose of 118–3520 J. Nd:YAG laser: scanning, 6–225 sec, 37–1350 J</td>
<td>Clinical/3 to 5 years</td>
<td>1.8% recurrence with Nd laser; 2.5% recurrence with Nd:YAG laser. Few cases of hypertrophic scar.</td>
</tr>
<tr>
<td>Ortiz et al.</td>
<td>(2014)</td>
<td>Open-label</td>
<td>10 pts/13 BCC</td>
<td>1 1064 nm, 80-120 J/cm², 10 ms, no cooling, 5 mm spot, 3 passes, 3 stacked pulses</td>
<td>Excision 30 days after laser tx</td>
<td>92% (12/13) clearance rate overall. At 120 J/cm², 100% (10/10) clearance rate.</td>
</tr>
</tbody>
</table>

**Side Effects**

- Minimal erythema
- Purpura
- Swelling
- Crusting
- Scar
- No severe adverse events

**Anticoagulation**

- Subjects with suboptimal response were currently on anticoagulation.
- Intravascular coagulation is important for effective treatment with vascular selective lasers.
- Anticoagulation may interfere with efficacy.

**Flaws**

- Confirmation of clearance rates with clinical exam or biopsy.
- Should use surgical excision.
- Bulk hyperthermia can cause nonspecific damage.
- Scar
- Lack of standardized treatment protocol.
- Varying number of treatments.
- Retrospective studies.
- Lack of control.
- Multiple treatments necessary.
AN EXPANDED STUDY OF LONG-PULSED 1064 NM ND:YAG LASER TREATMENT OF BASAL CELL CARCINOMA

Arisa Ortiz, Rox Anderson, Catherine DiGiorgio, Brian Jiang, Faiza Shafiq, Mathew Avram

1064 nm Laser Treatment of BCC

- 33 BCC tumors < 2.1 cm.
- Treatment settings:
  - One treatment
  - 1064 nm, 5-6 mm spot, 125 - 140 J/cm², 7-10 ms pulse duration
  - No cooling
  - No anesthesia
- Standard surgical excision with 5 mm margins 4 weeks following laser tx

Results

- 31 subjects completed the study
- BCC tumors had a 90% (28 of 31 BCC tumors) histologic clearance rate after one treatment with the long-pulsed 1064 nm Nd:YAG laser
- Treatments were generally well tolerated without any anesthesia
- No significant adverse events occurred

Histologic Evidence

Clearance Rates

- Rate of clearance of BCC following biopsy ~ 20%
- Data is well powered to reject the null hypothesis that laser treatment does not have an effect
- Laser treatment is at least comparable if not superior to common modalities
  - Methyl aminolevulinate (MAL)-PDT ~ 72.8%
  - Imiquimod cream ~ 83.4%
  - Fluorouracil cream ~ 89.1%
Advantages

- Potential for only one treatment visit
- Fast
- Easily tolerated without anesthesia
- No follow-up for suture removal
- No significant downtime
- No limitations on activity
- Minimal wound care

Advantages

- Relatively decreased risk for complications
- Infection, bleeding
- Biopsy scars may potentially improve
- Collagen remodeling from heating of the dermis
- Most patients would choose laser treatment over surgical excision

Alternative for treating patients with multiple tumors or those who are poor surgical candidates


VivoSight Dx OCT Images of Vascular Supply

Long-term Results

- 9 month f/u
- 5 month f/u
- 4 month f/u
My Recommendations

- Treat nonaggressive BCC tumors
  - Nodular, superficial, multifocal, pigmented
  - Avoid aggressive subtypes since treatment margins are not defined
  - Avoid tumors that fall under Mohs AUC
- Treat off the face
  - Exceptions – poor surgical candidate, multiple tumors
- Monitor for recurrence with regular skin checks

How to do it

- Treat with a standard 5 mm margin
- Lidocaine without epinephrine
  - To avoid vasoconstriction
- 1064 nm, 5 mm, 8 ms, 140 J/cm², no cooling
  - Lift off slightly to avoid cooling
- Pulse duration may vary based on device (8-10 ms)
- Let cool in between passes to avoid bulk heating
- Average 25-35 pulses depending on size

How To Do It

Immediate Endpoint

Slight Greying
Slight Contraction

How to Bill

- Billed as malignant destruction/EDC
- 17260-17266 trunk

Future Directions
**Nanotechnology**

- Antibody-targeted gold nanorod-directed laser therapy.
- GNR injected directly into the BCC tumor, Ab binds GNR to tumor.
- GNR absorb near-infrared light (1064 nm) and convert it to heat.
- Heat generation will specifically and preferentially kill tumor cells bound to GNR.

**PTCH Gene**


**HHIP**

- HHIP expression is up-regulated in BCC.
- HHIP is a surface protein with affinity to endogenous ligands (similar to Patched).
- HHIP binds with affinity to HH agonists as a competitive binding site.
- HHIP lacks a cytosolic signaling pathway so there is no known pharmacological consequence.

**Pre-Clinical Studies**

- ASZ001 mouse BCC (courtesy of Ervin Epstein, CHRCO).
- Positive Ab screen for anti-HHIP Ab on ASZ001 BCC Cells.

**In vivo Study**

- To measure diffusion and distribution after injection of Ab-targeted GNR into established BCC tumors in mice using in vivo imaging system of a fluorophore-labeled nanoparticle.
- Injected GNR suspension rapidly diffuses into the surrounding tissues.
- Fluorescence remained within the area of injection throughout the 48-hour study period.

**Murine Study**

- SCID mice with ASZ001 BCC tumors were injected with GNR.
- After 24 hours the test group tumors and non-injected controls were treated with 1064 nm laser.
- Control animals did not receive test article or laser energy.
- Mice were observed for 30 days for signs of tumor growth and/or recurrence, the mice were sacrificed, and histopathology of the tumor site and major organs was conducted.
Mouse Model Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number Treated</th>
<th>Cancer Free at 30 Days</th>
<th>Percent Cure at 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Laser Only</td>
<td>7</td>
<td>5</td>
<td>71%</td>
</tr>
<tr>
<td>Laser &amp; GNR</td>
<td>7</td>
<td>7</td>
<td>100%</td>
</tr>
</tbody>
</table>

- Laser only: fluence 140 J/cm², spot 5 mm and pulse width 8 ms, averaged 20 pulses at approximately 1 Hz
- Laser & GNR: fluence 60 J/cm², spot 5 mm and pulse width 5 ms, averaged 36 pulses at approximately 1 Hz

Ex vivo Porcine Skin Model

- The Ab-targeting GNR was further tested in porcine skin ex vivo to define determine optimal GNR concentration and laser settings
- One day prior to laser application, 0.05 mL of GNR was intradermally injected into a traced grid on pig skin
- GNR was allowed to diffuse overnight
- The 1064 nm Nd:YAG laser was focused onto the center of the diffused area of the skin where the GNR was injected
- A FLIR camera was focused on the injection site of the GNR for real-time photothermal imaging

GNR Concentration

- Evaluated the effects of varying the concentration of GNR
- Fluence - 60 joules/cm², the spot - 5 mm, pulse width - 5 ms, pulses - 36, 1 Hz
- The results suggest that the heat generated is log-linearly related to GNR concentration
- We intend to target an intradermal peak temperature of 60-70 °C, an optimum concentration of 0.03 mg/mL was chosen for further study

Optimal Laser Dosimetry

- Further Mouse Studies Underway
- Human Pilot Study

Conclusion

- Lasers and light-sources are a promising new non-invasive treatment approach for treating BCC
- Clearance rates are comparable to other topical modalities, ED&C, topical imiquimod
- Reasonable alternative for treating patients with multiple tumors or poor surgical candidates
- Nanoparticles may enhance results seen with laser treatment while decreasing side effects
- Further studies are warranted
Thank you!