Scalp Cooling to Prevent Chemotherapy-Induced Alopecia

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Baylor College of Medicine
Background

- Chemotherapy treats micro-metastatic disease & can decrease the risk of breast cancer recurrence

- It is associated with side effects such as chemotherapy-induced alopecia. Women rate this as one of the most severe, distressing and troublesome side effects

- Many countries use scalp cooling devices to prevent chemotherapy-induced alopecia with variable success rates based on non-randomized trials (25%-100% hair retention)
Scalp Cooling Devices Worldwide 2016

Note—this figure represents scalp cooling devices and does not include cold cap use

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History of Scalp Cooling

• 1970s
  – Tourniquets are utilized to reduce the blood flow to hair follicles during peak chemo
  – Worked but caused headache and nerve compression so no longer utilized

• Medications
  – AS101 (immune modulator) and Minoxidil reduced the duration of alopecia but did not prevent it
History of Scalp Cooling

• 1979
  – First US patent for Mark Barron’s “Chemo Cap” which was a resizable gel-filled nylon pouches that could be frozen. Patent expired in 1998. Studies from 1995-2003 showed some success with this approach

• 1997
  – First prototype of the Paxman Scalp Cooling System was used and installed in the Huddersfield Royal Infirmary
How Scalp Cooling Works

Borrowed/Courtesy of Corina van den Hurk
Netherlands Comprehensive Cancer Organization
How Scalp Cooling Works
Why Not Used In the US Sooner?

• Devices have more stringent and different approval processes which the cold caps did not have to go through

• The FDA had concerns about patient safety and the possibility of scalp metastasis. There are 2 large studies from other countries showing no increase in scalp metastasis or change in overall survival with device use.

• FDA approved the first scalp cooling device Dec 2015
  — This was a non-randomized trial and only looked at taxane-based chemotherapy.
  — Showed 66% hair retention.

Van den Hurk Breast 2013
Lemieux Breast Can Res 2015
Rugo ASCO poster 6/2015
Safety: Overall Survival

• Retrospective study of 1370 women with stage 1-3 breast cancer from Quebec
• Median f/u 6.3 years
• No difference in Overall Survival in scalp cooled vs no scalp cooling groups
Safety: Scalp Metastasis/Recurrence

- Overview from Munich cancer registry
- >33,771 breast cancer patients
- 77% treated adjuvantly, mainly with taxanes/anthracyclines
- Incidence not higher with scalp cooling
  - Scalp cooling 0.04-1%
  - No scalp cooling 0.03-3%

• 4 cases from MSKCC reported with grade 1-2 thermal injury to scalp
  – Penguin:
    • Case 1: Used alternative scalp covering (paper towel)
      – Blistering at upper mid forehead
    • Case 2: used appropriate protection
      – Blistering in forehead area
    • Case 3: crusting and desquamation of scalp
  – Elastogel: used after alopecia from AC, during paclitaxel
    • Large bulla on scalp

Belum et al, BCRT 2016
Table 1  Characteristics of patients with frostbite on the scalp following the use of cold caps

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age/Sex</th>
<th>Cancer</th>
<th>Chemo regimen</th>
<th>Cold cap usage details</th>
<th>Onset</th>
<th>Follow-up</th>
<th>Potential contributory factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>49/F</td>
<td>Breast</td>
<td>TCHP</td>
<td>Penguin™ 60'</td>
<td>Cycle 3</td>
<td>Mild persistent alopecia (at 5 months)</td>
<td>Lack of adequate padding between the cold cap and skin; duration of post-infusion cooling</td>
</tr>
<tr>
<td>2</td>
<td>55/F</td>
<td>Breast</td>
<td>AC → T</td>
<td>Elasto-Gel™ 15'</td>
<td>Cycle 3</td>
<td>Mild persistent alopecia (at 4 months)</td>
<td>Pre-existing alopecia; lack of padding; duration of post-infusion cooling</td>
</tr>
<tr>
<td>3</td>
<td>58/F</td>
<td>Breast</td>
<td>PH</td>
<td>Penguin™ 50'</td>
<td>Cycle 4a</td>
<td>Alopecia resolved (at 2 months)</td>
<td>Pre-existing diffuse alopecia; duration of post-infusion cooling</td>
</tr>
<tr>
<td>4</td>
<td>50/F</td>
<td>Breast</td>
<td>CMF</td>
<td>Penguin™ 50'</td>
<td>Cycle 1</td>
<td>Mild persistent alopecia, skin sensitivity (at 6 months)</td>
<td>Lack of adequate padding; duration of post-infusion cooling</td>
</tr>
</tbody>
</table>
• Demonstrate the safety and efficacy of scalp cooling devices in reducing chemotherapy-induced alopecia

• SCALP is the first randomized trial in the world to evaluate modern scalp cooling
SCALP

• December 2013 – September 2016
• Open at 7 sites across the US
  – 3 academic centers
  – 4 community oncology clinics
• 229 women signed consent
Key Eligibility

**Inclusion Criteria**
- Stage 1 or 2 breast cancer
- Neoadjuvant or adjuvant chemotherapy

**Exclusion Criteria**
- Migraines
- Anemia
- Hypothyroidism
- Other uncontrolled medical conditions
Design

Enrollment → Randomization →

Scalp Cooling Device → Control

Assessed for:
• Alopecia
• Quality of Life
• Device Safety
Scalp Cooling Device Arm
Alopecia Grading: CTCAE Version 4.0

Grade 0
No hair loss

Grade 1
Hair loss of up to 50% of normal, no wig required

Grade 2
Hair loss of > 50% of normal, wig required

CTCAE = Common Terminology Criteria for Adverse Events Version 4.0

* CTCAE only defines alopecia through Grade 2
Pictorial Tool

Grade 0
No significant hair loss.

Grade 1
Hair loss of up to 50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss but it does not require a wig or hair piece or camouflage.

Grade 2
Hair loss of >50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss associated with psychosexual impact.
Examples of Grading

**Baseline**
(Grade 0 alopecia)

**Grade 1 Alopecia**
* 3-4 weeks after using cooling system for 4 cycles of chemo
Examples of Grading

Baseline
(Grade 0 alopecia)

Subject in control group; 3 weeks after 2nd cycle of chemotherapy.

Grade 2 Alopecia

Subject in cooling group; 3 weeks after using cooling system for 2 cycles of chemotherapy.
**Design**

### Patient Reported Comfort Scale

<table>
<thead>
<tr>
<th>Comfort Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Comfortable</td>
</tr>
<tr>
<td>Reasonably Comfortable</td>
</tr>
<tr>
<td>Comfortable</td>
</tr>
<tr>
<td>Uncomfortable</td>
</tr>
<tr>
<td>Very uncomfortable</td>
</tr>
</tbody>
</table>

### Questionnaires

- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30
- Hospital Anxiety Depression Scale
- Body Image Scale

*European Journal of Oncology Nursing, 2004; 8: 121-130*
• 235 subjects were planned to be enrolled to provide 85% power to detect a 20% difference in hair preservation.

• The trial stopped early based on a pre-planned interim analysis for efficacy after 142 participants were evaluable for the primary endpoint with an O’Brien-Fleming spending function*
Statistical Analysis Plan

• Secondary endpoints included
  – Wig/scarf use
  – Quality of life
  – Hair preservation at completion of chemotherapy

• Study participants will be followed for 5 years post-study for time to first recurrence, overall survival, and site of first recurrence

Participant Flow Chart

293 Participants Consented

Why ineligible?
- Hypothyroidism (11)
- Anemia (10)
- Stage 3 Breast Cancer (7)
- Baseline Alopecia (5)
- Migraines (4)
- Age >= 70 (3)
- Lichens Planus (2)
- Other (6)

236 Randomized

Why withdrew consent?
- 18 Randomized to Control
  - 7 due to hair loss
  - 6 in pre-cooling phase
    - 4 Device (cold/discomfort)
    - 1 Anxiety
    - 1 Claustrophobia
- 4 during chemo (device cold)
- 2 alternate treatment
- 3 withdrew consent
- 1 chemo related
- 1 progressive disease

157 Device

130 Modified ITT

79 Control

54 Modified ITT
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cooling</th>
<th>Non-Cooling</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=130</td>
<td>N=54</td>
<td>N=184</td>
</tr>
<tr>
<td>Age (years) Mean (SD)</td>
<td>50.4 (10.5)</td>
<td>51.7 (10.1)</td>
<td>50.8 (10.4)</td>
</tr>
<tr>
<td>Race [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>106 (81.5%)</td>
<td>41 (75.9%)</td>
<td>147 (79.9%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>16 (12.3%)</td>
<td>8 (14.8%)</td>
<td>24 (13%)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (3.8%)</td>
<td>5 (9.3%)</td>
<td>10 (5.4%)</td>
</tr>
<tr>
<td>Ethnicity [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>20 (15.4%)</td>
<td>9 (16.7%)</td>
<td>29 (15.8%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>108 (83.1%)</td>
<td>45 (83.3%)</td>
<td>153 (83.2%)</td>
</tr>
<tr>
<td>Major Chemotherapy Type [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline</td>
<td>45 (34.6%)</td>
<td>23 (42.6%)</td>
<td>68 (37%)</td>
</tr>
<tr>
<td>Taxane</td>
<td>85 (65.4%)</td>
<td>31 (57.4%)</td>
<td>116 (63%)</td>
</tr>
<tr>
<td>Breast Cancer Stage [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>50 (38.5%)</td>
<td>19 (35.2%)</td>
<td>69 (37.5%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>80 (61.5%)</td>
<td>35 (64.8%)</td>
<td>115 (62.5%)</td>
</tr>
</tbody>
</table>
Results: Primary Outcome

Hair Preservation After 4 Cycles of Chemotherapy

- Cooling
  - Success: 53.1% (44.5%, 61.4%)
  - Failure: 0% (0%, 6.6%)

- Non-cooling
  - Failure: 100%

Fisher's exact test p<0.0001

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Results: Primary Outcome

Hair Preservation in the Cooling Group (after 1st 4 cycles)

- **TAXANE**
  - Success: 63% (35%, 84.4%)

- **ANTHRACYCLINE**
  - Failure: 24.1% (8.6%, 51.6%)

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## Results: Adverse Events

### Adverse Device Effects: All Grade 1 or 2

<table>
<thead>
<tr>
<th>AADEs (CTCAE V4.0)</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6-8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=137)</td>
<td>n=117</td>
<td>n=90</td>
<td>n=83</td>
<td>n=36</td>
<td>n=31</td>
</tr>
<tr>
<td>Headache</td>
<td>11.7%</td>
<td>8.5%</td>
<td>1.1%</td>
<td>4.8%</td>
<td>5.6%</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.4%</td>
<td>1.7%</td>
<td>1.1%</td>
<td>1.2%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<3% rate of dizziness, ear pain, scalp pain, sinus pain, pruritus, and dry skin
<1% rate of chills, jaw pain, paresthesia, skin and SC tissue disorder, and skin ulceration
## Results: Quality of Life

### Patient Reported Comfort Scale

<table>
<thead>
<tr>
<th>Comfort Scale</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
<th>Cycle 4</th>
<th>Cycle 5</th>
<th>Cycle 6</th>
<th>Cycle 7</th>
<th>Cycle 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=137</td>
<td>n=117</td>
<td>n=90</td>
<td>n=83</td>
<td>n=36</td>
<td>n=31</td>
<td>n=11</td>
<td>n=9</td>
</tr>
<tr>
<td>Very Comfortable</td>
<td>10.9%</td>
<td>15.4%</td>
<td>13.3%</td>
<td>15.7%</td>
<td>16.7%</td>
<td>12.9%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reasonable</td>
<td>51.8%</td>
<td>41.9%</td>
<td>50%</td>
<td>45.8%</td>
<td>50%</td>
<td>54.8%</td>
<td>45.5%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Comfortable</td>
<td>27.7%</td>
<td>27.4%</td>
<td>22.2%</td>
<td>27.7%</td>
<td>22.2%</td>
<td>29%</td>
<td>36.4%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Uncomfortable</td>
<td>8%</td>
<td>10.3%</td>
<td>12.2%</td>
<td>9.6%</td>
<td>8.3%</td>
<td>3.2%</td>
<td>9.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Very Uncomfortable</td>
<td>-</td>
<td>3.4%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9.1%</td>
<td>-</td>
</tr>
<tr>
<td>Not Assessed</td>
<td>1.5%</td>
<td>1.7%</td>
<td>2.2%</td>
<td>1.2%</td>
<td>2.8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Quality of Life Assessments showed no difference

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## Secondary Endpoints

<table>
<thead>
<tr>
<th>Wig or Scarf Use</th>
<th>Cooling</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>33.9%</td>
<td>0%</td>
</tr>
<tr>
<td>Yes</td>
<td>44.6%</td>
<td>68.5%</td>
</tr>
<tr>
<td>Unknown (had grade 2 alopecia)</td>
<td>20%</td>
<td>31.5%</td>
</tr>
</tbody>
</table>
Secondary Endpoints

Hair Preservation in the cooling group at the end of chemotherapy

- **ALL**: 46.2% (37.8%, 54.7%) with n=130
- **TAXANE**: 64.6% (53.8%, 74.1%) with n=82
- **ANTHRACYCLINE**: 0% (0%, 56.1%) with n=3
- **BOTH**: 15.6% (7.7%, 28.8%) with n=45

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## Secondary Endpoints

### Hair Retention by Regimen After Completion of Chemotherapy in Cooling Arm

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>% Successful Hair Preservation (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin 60mg/m2 with cyclophosphamide 600mg/m2</td>
<td>0% (3)</td>
</tr>
<tr>
<td>Adriamycin 60mg/m2 with cyclophosphamide 600mg/m2 + Docetaxel 100mg/m2</td>
<td>0% (3)</td>
</tr>
<tr>
<td>Adriamycin 60mg/m2 with cyclophosphamide 600mg/m2 + Paclitaxel 80-90 mg/m2 weekly with carboplatin AUC of 6 every 3 weeks</td>
<td>66.7% (3)</td>
</tr>
<tr>
<td>Adriamycin 60mg/m2 with cyclophosphamide 600mg/m2 + Paclitaxel 80mg-90/mg/m2 weekly</td>
<td>18.8% (16)</td>
</tr>
<tr>
<td>Adriamycin 60mg/m2 with cyclophosphamide 600mg/m2 + Paclitaxel 175mg q2 weeks</td>
<td>40% (20)</td>
</tr>
<tr>
<td>Doxorubicin 50mg/m2 with 5-Fluorouracil 500mg/m2 and cyclophosphamide 500mg/m2 + Paclitaxel 80mg-90mg/m2 weekly</td>
<td>100% (1)</td>
</tr>
<tr>
<td>Doxorubicin 50mg/m2 with 5-Fluorouracil 500mg/m2 and cyclophosphamide 500mg/m2 + Paclitaxel 175mg/m2 q2 weeks</td>
<td>0% (1)</td>
</tr>
<tr>
<td>Paclitaxel 80mg/m2 - 90mg/m2 weekly (every 3 weeks constitute a cycle), or 175mg/m2 every 2-3 weeks as a single agent</td>
<td>100% (7)</td>
</tr>
<tr>
<td>Paclitaxel 80-90 mg/m2 weekly with carboplatin AUC of 6 every 3 weeks</td>
<td>100% (1)</td>
</tr>
<tr>
<td>Docetaxel 75mg/m2 - 100mg/m2 with pertuzumab/trastuzumab + Adriamycin 60mg/m2 with cyclophosphamide 600mg/m2</td>
<td>0% (1)</td>
</tr>
<tr>
<td>Docetaxel 75mg/m2 with cyclophosphamide 600mg/m2</td>
<td>56.5% (46)</td>
</tr>
<tr>
<td>Docetaxel 75mg/m2 with carboplatin AUC of 6 and trastuzumab at standard doses</td>
<td>75%(28)</td>
</tr>
</tbody>
</table>
Conclusion from SCALP trial

- Scalp cooling devices are highly effective
- This device received FDA clearance in the US based on these data
- Need further studies exploring this technology for other types of tumors
- More studies for impact of chemotherapy-induced alopecia on psyche and body image
- Tailored QOL tools are needed to evaluate the impact of alopecia