Australian Implementation of scalp cooling for prevention of chemotherapy induced alopecia.

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Disclosures

Devices have been loaned by Dignitana and Paxman prior to purchase.
Hair loss from chemotherapy

- Associated with significant distress
  - Visibility “the cancer look”
  - Altered body image and sexuality
  - Inconvenience, cost and discomfort of wigs
- May lead to decision to reject chemotherapy
- Van den Hurk cohort (Netherlands) n=266 breast cancer patients (n=89 no SC)
  - Rank 1 or 2 of 26 side effects on t= before, 3wk and 6 m after chemotherapy
  - Impact difficult to measure on standard QOL forms as minimal questioning on alopecia
  - “Why ask when nothing can be done about it”

Alterations in hair after chemotherapy

- Altered regrowth due to follicle damage
  - Softer, curlier, “like baby hair”, “a bad perm”
  - Depigmentation due to melanocyte injury

- Permanent alopecia resistant to treatment
  - Case series (?1%) with FEC-D
  - Case reports of permanent loss with TCarboH, Taxanes alone
  - Probably due to follicle stem cell injury
  - Consider unmasking of androgenic, hypothyroid or autoimmune alopecia as contributing factors

Pathobiology of chemotherapy-induced hair loss

Ralf Paus, Iain S Haslam, Andrey A Sharov, Vladimir A Botchkarev

Hair loss can be a psychologically devastating adverse effect of chemotherapy, but satisfactory management strategies for chemotherapy-induced alopecia remain elusive. In this Review we focus on the complex pathobiology of this side-effect. We discuss the clinical features and current management approaches, then draw upon evidence from mouse models and human hair-follicle organ-culture studies to explore the main pathobiology principles and explain why chemotherapy-induced alopecia is so challenging to manage. P53-dependent apoptosis of hair-matrix keratinocytes and chemotherapy-induced hair-cycle abnormalities, driven by the dystrophic anagen or dystrophic catagen pathway, play important parts in the degree of hair-follicle damage, alopecia phenotype, and hair-regrowth pattern. Additionally, the degree of hair-follicle stem-cell damage determines whether chemotherapy-induced alopecia is reversible. We highlight the need for carefully designed preclinical research models to generate novel, clinically relevant pointers to how this condition may be overcome.

Introduction
Few adverse effects of chemotherapy generate as much trepidation as the often substantial and sudden hair loss that can be induced by selected chemotherapeutic agents. Although some treatment options, such as scalp cooling, show a degree of efficacy in specific chemotherapy regimens (eg, taxane monotherapy), many are unsatisfactory. As such, chemotherapy-induced alopecia represents one of the major unmet challenges in clinical oncology. Extreme anxiety related to this cosmetic disfigurement reportedly drives 8% of patients to reject and women have widespread chemotherapy-induced alopecia more frequently than any other pattern. Hair-shaft shedding, which manifests as anagen effluvium or telogen effluvium, begins days to weeks after the initiation of many, although not all, chemotherapeutic agents. The visible hair loss results from defined disturbances of normal hair-shaft production and of hair-follicle cycling (figure 1). Reversibility of alopecia depends on the degree of hair-follicle stem-cell damage.

The risk of chemotherapy-induced alopecia and the degree of hair loss differ substantially between

Paus et al, Lancet Oncology, Feb 2013, Vol 14
Each Cycle of chemo leaves a mark
Fragile hair prone to breakage
Scalp Cooling for prevention of CIA

- **Lowering scalp temperature below 22 degrees reduces**
  - Blood flow to the scalp during peak chemotherapy exposure
  - Metabolic activity of hair follicles
  - Hair loss particularly after first cycle, with reduced need for wig / head covering

- **Challenges include**
  - Avoiding overcooling with pain “ice cream headache” and “frost bite” of skin
  - Tendency to warm up again with application to the body
    - Requires either frequent changes or circulation of coolant
  - Duration of chemotherapy infusion
  - Combinations of drugs with high alopecia potential eg TAC
  - Frequency of administration of drugs eg daily vs weekly vs 3 weekly
  - Ensuring no increase in frequency of scalp metastases

Penguin Cold Caps

- Caps stored in freezer at -35°C
  - Occupies significant space
- Changed every half hour before, during and after infusion
  - Up to 10 per patient, nursing time to change or “cap buddy”
  - Longer chair time, patient scheduling changes
- Some discomfort as it goes on already cold
  - Patient may reject therapy at this time
- Reported Efficacy with TC x 4-6
  - > 50% Dean’s alopecia grade 1-2
  - More hair loss at periphery than crown

Rugo H et al, SABCS 2012
- Swedish company
- Widely used in Europe
- US randomised trial underway
- Machine circulates cold fluid into cap
  - Sits between 2 chemo chairs
  - Tubing can be disconnected for a short time
  - Coolant temperature can be monitored 2-5°C
  - Not cold when cap fitted so more comfortable
  - Cap not changed during treatment but need to ensure tight fit on crown
  - ½ hour pre-cooling
  - Post cooling 1-2 hours depending on regimen
- TGA approved in Australia and marketed by Aurora Bioscience

UK based family company

Widely used in UK and Netherlands

US randomised trial underway

Similar concept to Dignicaps

Smaller unit

Temperature not monitored on cap

Need to ensure tight fit on crown

Marketed in Australia by Regional Health Care Group
Why not effective for all patients?

Result depends on

› Type and dose of chemotherapy
  - Shorter schedules better
  - TAC unsuccessful
  - Higher dose = worse

› Age: older = worse

› Type of hair determined by race: African/Asian = worse

› Patient comfort and choice – “bad hair” vs “no hair”

No influence: dampening of hair, previous chemotherapy, length/quantity hair, dying/waving/colouring

Hurk van den CJG et al. Scalp cooling hair preservation and associated characteristics in 1411 chemotherapy patients - Results of the Dutch Scalp Cooling Registry. Acta Oncologica 2012, 51:491
Metastatic Breast Cancer

- Many women have lost their hair before
  - “I am not going to die bald”
  - May restrict choices of therapy
- 3 weekly Docetaxel 75 g/m2 suitable
- Weekly paclitaxel or nab-paclitaxel may be suitable
  - More chair time
- Consider previous radiotherapy and hepatic function
- Eribulin under investigation
  - Short infusion time (5 mins)
  - Testing half hour pre and post cooling
Mater Sydney Audit Experience

- Initiative of NUM Kerrie Andrews in 2010 to introduce Penguin Cold Cap system
  - Donated by The Friends of the Mater Foundation
  - Commenced with early breast cancer adjuvant chemotherapy

2012/13 Dignitana introduced
2014 Paxman introduced

Now offered to
- All suitable women with early breast cancer receiving AC/ TC/ FEC-D +/- H
- Selected metastatic prostate / breast cancer patients receiving taxanes
Completion Rates Gradually improving

Reasons for non-completion

› ‘could not tolerate the cold’ or ‘pain’
› Significant hair loss early in treatment so stopped mid-way through chemotherapy
› other issues
  - Nausea
  - Low BP (vagal)
  - Changes in chemotherapy due to other side effects

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Completion Rate</th>
</tr>
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<tbody>
<tr>
<td>Penguin</td>
<td>70%</td>
</tr>
<tr>
<td>Dignitana</td>
<td>80.5%</td>
</tr>
<tr>
<td>Paxman</td>
<td>89%*</td>
</tr>
</tbody>
</table>

*Chi sq 6.4 df=2 p=0.04
58 (57%) of patients in the FEC / FEC-D group recorded a Dean’s Grade 3/4 (over 50% hair loss)

50 (40%) of patients in the TC group recorded a Dean’s Grade 3/4

More patients have high grade hair loss in the FEC/ FEC-D group compared with patients in the other three treatment groups (Chi-square=28.8, df=6, p<0.0005)

- 6 vs 4 cycles contributes?
Which system is preferred?

- 57 (45%) of patients in the Penguin group recorded a Dean’s Grade 3/4 (over 50% hair loss)
- 61 (50%) of patients in the Dignitana group recorded a Dean’s Grade 3/4
- 11 (42%) of patients in the Paxman group recorded a Dean’s Grade 3/4
  - No statistically significant difference in hair loss
  - Spread of chemotherapy regimens not controlled

- Nursing staff strongly preferred the coolant systems
  - Avoids need for cap changes
  - Greater patient comfort
  - Emphasised issues of crown contact
  - Paxman / Dignitana similarly easy to use
  - Need to do 2 cycles before discontinuing as most hair loss is in cycle 1
Informal Patient Feedback

› “I was able to hide my breast cancer diagnosis from my work colleagues and children.”
› “It helped me take a little control at a chaotic time.”
› “The cold gloves were worse.”
› “I have lost a lot of hair but can get by with using a cap to cover the crown.”
› “The heated blankets were essential.”
› “The regrowth is very fast.”
› “No-one is cutting me any slack because I don’t look sick!”
Dual aims

› To assess the impact of hair loss in order to develop a Patient Reported Outcome Measure for CIA
- Part of an international collaboration with Netherlands and UK
- Better tools are needed for clinical trials

› To assess the impact of scalp cooling and patient experiences at the Mater
- Motivations
- Expectations
- Tolerability
- Outcomes and satisfaction
- Unmet needs for information and support

A O’Reilly, J Shaw, B Baylock, L Pugliano, J Winstanley, F Boyle, P Butow
Recruitment process & Informed Consent

- The Patricia Ritchie Centre identified potential participants from their patient database, purposefully sampling to include both patients who had undergone scalp cooling and patients who had not.

- Breast cancer patients only were included in the study.
  - Receiving regimens with a high potential for chemotherapy induced hair loss.

- Consent procedures and collection of demographic and clinical characteristics were collected and collated by Patricia Ritchie Centre and provided to PoCoG.
  - Ethics approval St Vincents Hospital HREC [SVH 13/254]

- Recordings transcribed and analysed by Brandi Baylock and Joanne Shaw (POCOG)
  - Thematic analysis performed using NVIVO software
17 patients participated in the study
- Median age 55 years (range 43-74)
- 11 had completed scalp cooling, with Penguin (5), Paxman (1) and Dignitana (5) devices
  - Variable hair loss grade 1-3
- 6 had not been scalp – cooled, and all have experienced Grade 4 hair loss
  - Chemotherapy not suitable
  - Declined
  - Device not available
Theme 1: Perceptions of hair loss as a motivation for scalp cooling

- Illness representation and self-image were strong motivators
  
  *I think that hair loss is something that's really, really important to a women in particular and I'm wondering if I sense that because it could have happened to me and didn't and so I realise how significant it is for me because I'm extremely grateful for the fact that I had that opportunity. I just think that I've been blessed with that option*

  A reminder from me every time I look at myself in the mirror, that I’m actually sick.

- More concern about managing other people’s reactions to their hair loss
  
  *it didn’t bother me but it bothered my children, and then so I got my husband to shave it as well.*

- For a small number of participants scalp cooling offered hope and control in a generally uncontrollable situation
  
  *Do you know what? It gives you one little layer of control I was assuming I was going to lose it, and then it was like a life raft...*
Theme 2: Information needs

- Participants received efficacy information from oncologists and were satisfied with the level of information received. *My oncologist said that if you use the cold caps, when you start your chemo, it will thin out… and that's what I kind of expected. I didn't know anything more after that. Like the condition of the hair or anything like that.*

- NSC participants did not recall scalp cooling being included in treatment decision-making discussions and therefore perceived they were not given an option to consider. *I wasn't told directly about it, but I made friends with another woman at the time…and she was saying, "I'm really hoping to get it cold cap." And I thought what's the cold cap? So I asked the breast care nurse, and then she said yes, but I, think the program is full up for the moment.*

- Less satisfaction with the information provided regarding hair care during scalp cooling or what to expect ie the level of discomfort was unexpected for many. *My issue more is around how to care for the hair.*

- Written information is lacking. *Some of it was a little bit confusing. Like, the timeframe for this and that and what type of shampoo and conditioning you should use when.*
Theme 3: Expectations vs Experience

- Scalp Cooled participants were aware that there was a risk of hair loss however there was a mis-match between expectations of hair loss and patient experience. 
  *When I was going through the cooling, I thought my hair would just stay pretty.. That kind of buoyed by right through, and it did. I got anxious when bits did come out, or when I was trying very hard to not to touch it too much or anything when things came out. So there were anxious moments, but I could still go out and do my things and meet people and feel vaguely okay.*

- Several participants reportedly experienced tolerability issues that they were unprepared for. 
  *My lips were blue…I couldn't concentrate, I couldn't read - well, you can't hear either. It wasn't worth having anyone sit with me because I couldn't have a conversation.*

- Regrowth was an important factor for continuing to scalp cool after hair loss. 
  *Well, I was a bit concerned because I was losing lots of hair, but Kerrie kept saying, "No, keep it up. You won't lose much more. When your hair does grow back, it'll grow back quicker than if you don't." And it did.*

- Despite their initial expectations with respect to hair loss not being met, the majority of scalp cooled participants were satisfied with their treatment decision.
Theme 4: Decision Making

• Scalp cooled participants highlighted treatment delays, extra time per cycle and side effects as well as the opinions of others as potentially influencing decision-making around scalp cooling and highlighted the need for more information about what to expect.

  When I got to the end and I looked in the mirror I was quite glad that I had hair.

  You know, I found it really very painful. I'm very sensitive to cold anyway, so that was really quite challenging.

• Non-scalp cooled participants highlighted efficacy, tolerability and additional time per cycle as factors that would need consideration.

  I would have liked to but because it was urgent to start and it was – the queue was too long for scalp cooling.
POTENTIAL IMPLICATIONS

- Managing other people’s reactions to hair loss was the primary motivation for the majority of patients undergoing scalp cooling. Self-image was less important to both scalp cooled and non-scalp cooled participants.

- Information was highlighted as an important driver of patient expectations. More detailed information outlining what to expect and how to manage scalp cooling is required. This information needs to include information that can be supplied to hairdressers and those supplying wigs and headcovers.

- The information provided about efficacy or the way in which it was presented may also explain the high level of expectation amongst the scalp cooled group that hair loss would only be minimal.

- Engagement with the wider cancer care community of health professionals including Look Good Feel better and hairdressers.

- Further research is required to understand the degree to which the themes identified in this study reflect the views of patients more generally with respect to scalp cooling.
Practical tips

› Nursing staff championed the initial implementation
› Additional advice on hair care during treatment needed
› Scheduling critical with 4 hour time blocks on chairs
  - Reorganised work flows so cooling is set up first thing in the morning
    - Patients need to be reviewed by their oncologists early
  - Short weeks eg Easter and Christmas challenging
    - Sometimes delay starting chemotherapy for up to a week
› Managing expectations important
› Conditioner and dampening helps fit of caps
› Heated blankets for comfort

› Support of and feedback to donors critical
  - Put a plaque on it and take a photo
Research Directions

› **Variable efficacy**
  - Standard post cooling times may not cover variability in pharmacokinetics
  - Genetic / ethnic differences in metabolism
  - Drug doses and combinations
  - Different hair types
  - Comorbidities eg thyroid
  - Androgenic alopecia

› **Hair care** during treatment
  - Colouring
  - Cutting / hairdressing
  - Optimal length

› **New international QOL tool** being developed
  - Existing QOL tools poorly sensitive to effects of partial hair loss found with scalp cooling
  - Focus groups recently completed at Mater

› **Safety**
  - Extensive data collection in Canada and Netherlands does not indicate increased risk of scalp metastases but ongoing audit important

› **Benchmarking**
  - International data items being developed
  - Software under development for web-based system to capture results (POCOG)

› **Pathophysiology**
  - Cell cycle / gene changes in follicles

› **System change**
  - Presentations at National and state clinical meetings (MOGA, COSA, CNSA, WACOG, VCOG)
  - Survey of barriers / facilitators underway (POCOG)
Implementation checklist

› Suitable patient population? – breast, prostate, lung, ovarian, colorectal
› Research or benchmarking pathway? – ethics and protocol vs clinical audit
› Institutional support for implementation
› Nurse champion to lead the implementation – visit Mater if desired
› Space for devices in treatment area
› Ability to accommodate longer chair times - step down area possible?
› Which device? – Dignitana (Aurora) or Paxman (Regional Health Care)
› Funding for devices – local donors, Dry July, Movember
› Education of oncologists and surgeons about patient selection / expectations
› Infection control and device safety sign off
› Hair care – conditioner, wetting, information for patients and hairdressers