CLINICAL STUDY PROTOCOL

A hair loss prevention study for patients with advanced pancreatic cancer utilizing scalp cooling

Protocol Number

HRI-ScalpCooling-001

Sponsor

HonorHealth Research Institute

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version 5

Confidentiality Statement:

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Synopsis

Primary Objective

At the end of three, 3 week cycles of chemotherapy, patients will experience hair preservation defined as grade 0 or 1 alopecia, versus grade 2, as defined by CTCAE Version 5.0.

Secondary Objectives (if applicable)

To determine patient comfort while receiving scalp cooling, using the Paxman scalp cooling device, by asking one Likert scale question.

To determine reasons for patient report of "uncomfortable" or "very uncomfortable" during the scalp cooling period asking one qualitative question.

To identify chemotherapy-induced alopecia distress by utilizing the Chemotherapy-Induced Alopecia Distress Scale (CADS). The CADS instrument is a valid and reliable tool for measuring distress of chemotherapy-induced alopecia. The total score is calculated by summing the response for all items. The higher the score, the more distress related to chemotherapy-induced alopecia. Excellent internal consistency, indicating reliability, was found with Cronbach's alpha coefficient =0.95 for the total. The findings were similar with the validation dataset, showing external validity (1).

References

a. Authors: Cho, J., Choi, IR., Kim, YH., Im, YH., Park, S., Lee, S., Lee, JH., Yang, SJ. Title: Development and validation of Chemotherapy-Induced alopecia distress scale (CADS) for breast cancer patients. Publication: Annals of Oncology Publication date: 2014; Issue: 25(2):Page/Line: 346-351. doi: 10.1093/annonc.mdt476.

Study Duration

Patients will participate in the study until the end of three, 3 week cycles of chemotherapy.

Duration of overall study will be approximately 9 months. The plan is to accrue up to 15 patients with a minimum of 10 evaluable after 3 cycles of treatment.

Study Design

This is a pilot, feasibility study using a convenience sample. Sample size is not based on a priori power analysis.

Descriptive statistics will be utilized.

One arm, repeated measures design where hair loss in each patient will be determined from baseline with the goal of hair preservation.

The response of the patients will be compared to a historic control where it is known that 100% of patients receiving this regimen who do not use scalp cooling will experience grade 2 alopecia.

The pilot will be considered a success if ≥ 30% of the participants have grade 0 or 1 alopecia at the end of the study as grade 2 alopecia has been seen in 100% of the patients receiving the combination of nab-paclitaxel, gemcitabine and cisplatin.

Study Population

Inclusion Criteria:

- Willing and able to provide written informed consent/assent for the trial
- ≥18 years of age on day of signing informed consent
- Diagnosis of pancreatic cancer and scheduled to receive treatment consisting of a regimen containing nab-paclitaxel, gemcitabine and cisplatin

Exclusion Criteria:

- Grade 1 or 2 alopecia
- Existing history of scalp metastases or the presence of scalp metastases is suspected
- Cancers of the head and neck
- CNS malignancies (either primary or metastatic)
- Cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia, cold migraine, cold urticaria, post-traumatic cold dystrophy
- Hematological malignancies (leukemia, non-Hodgkin and other generalized lymphomas) or hematological malignancies that are being treated for cure
- Imminent bone marrow ablation chemotherapy
- Imminent skull radiation
- Previously received or scheduled to undergo skull irradiation
- Severe liver or renal disease from any etiology as patient may not be able to metabolize or clear the metabolites of the chemotherapeutic agent
- Skin cancers including melanoma, squamous cell carcinoma and Merkel cell carcinoma
- Small cell carcinoma of the lung
- Solid tumors that have a high likelihood for metastasis in transit
- Squamous cell carcinoma of the lung

Number of Participants Enrollment up to 15 patients with 10 evaluable patients defined as those who have completed three, 3 week cycles of chemotherapy
Number of Study Sites One study site
Primary Outcome Variables The primary efficacy end points are successful hair preservation assessed using the Common Terminology Criteria for adverse events version 5.0 at the end of three cycles of chemotherapy
Secondary and Exploratory Outcome Variables (if applicable) Secondary endpoints include reported comfort during scalp cooling and scores on Chemotherapy-Induced Alopecia Distress Scale (CADS)
Visit Schedule Table (Optional)
Study Flow Chart (optional) N/A

Abbreviations

Abbreviation	Explanation
ADL	Activity of Daily Living
AE	Adverse Event
CADS	Chemotherapy-Induced Alopecia Distress Scale
CTCAE	Common Terminology Criteria for Adverse Events
EOT	End of treatment
ICF	Informed Consent Form
IRB	Institutional Review Board
SAE	Serious Adverse Event

Glossary of Terms

Glossary	Explanation

Table of Contents

1 - Introduction

1.1 Introductory Statement

This pilot feasibility study is intended for hair preservation in patients with pancreatic cancer who are receiving treatment containing nab-paclitaxel, gemcitabine and cisplatin.

2 - Background

2.1 Background/prevalence of research topic

It is known that chemotherapy may lead to alopecia. Researchers have found that scalp cooling can be used to reduce chemotherapy-induced alopecia, with minimal adverse treatment effects.

Nangia et al (2017) conducted a multicenter randomized clinical trial to assess hair preservation in women with breast cancer who utilized scalp cooling with the Paxman scalp cooling device while receiving a taxane, anthracycline or both. Scalp cooling occurred 30 minutes prior to chemotherapy infusion, during infusion of chemotherapy and 90 minutes following chemotherapy administration. The women who utilized scalp cooling were significantly more likely to have less than 50% hair loss following the completion of four cycles of chemotherapy. All adverse effects related to the cooling device were either a grade 1 or grade 2 and consisted of the following: chills, dizziness, headache, scalp pain, nausea, paresthesia, pruritus, sinus pain, skin and subcutaneous disorders, and skin ulcerations (2).

Vasconcelos et al (2018) also studied scalp cooling using the Paxman device in patients with breast cancer who were receiving anthracycline/taxane-based chemotherapy. Scalp cooling occurred 30 minutes prior to chemotherapy infusion, during infusion of chemotherapy and 90 minutes following chemotherapy administration. They found that scalp cooling was effective in preventing hair loss in this patient population. The majority of the participants reported they were reasonably comfortable while receiving scalp cooling (3).

Lemieux et al (2009) conducted a retrospective study of 640 patients with breast cancer. 553 of these patients used scalp cooling. The follow up time for those using scalp cooling was 5.8 years compared to 5.4 years for the control group. In the scalp cooling group, there was a 1.1% reported incidence of scalp metastases compared to the 1.2% reported incidence in the control group (4) .

Van den Hurk et al (2013) conducted a systemic review of 12 studies and the Munich Cancer Registry. 6,035 of the 48,711 patients with breast cancer used scalp cooling. Follow up was 2.2-9 years for the scalp cooling group compared to the 3-9.2 years for the control group. The scalp cooling group had a reported incidence of scalp metastases of 0.04%-1% compared to the control group with a 0.3%-3% reported incidence(5) .

According to the National Cancer Institute, it is estimated that over 56,000 new cases of pancreatic cancer will be diagnosed in 2019. In patients with pancreatic cancer, scalp metastasis is extremely rare and as of April 2019, there are very few reports in the literature. In 2013, Bdeiri and Kamar reported a patient with pancreatic cancer who presented with scalp metastasis. Their review of the literature revealed only 4 other reported similar cases (6).

2.2.1 Device Preclinical Experience

Chemotherapy targets rapidly dividing cells in the body, including hair. The hair follicles in the growth phase are attacked, resulting in hair loss approximately 2 weeks after the commencement of the chemotherapy treatment.

During scalp cooling with the Paxman scalp cooling device, the patient wears a specially fitted cap. The scalp is cooled prior to, during and after the administration of chemotherapy. This cooling causes vasoconstriction, reducing blood flow to the hair follicles with the intent of preventing or minimizing hair loss.

2.2.2 Device Clinical Experience

In a study conducted by Nangia, et al (2017) the researchers found that patients with breast cancer who used the Paxman Scalp Cooling device were significantly more likely to have less than 50% hair loss after the fourth chemotherapy cycle when compared to patients who did not use scalp cooling. 142 patients were evaluable during the interim analysis. 48 of the 95 patients using Paxman scalp cooling had successful hair preservation compared to 0 of the 47 women not using scalp cooling (2).

Additionally, a prospective observational study conducted by Vasconcelos et al (2018) found Paxman scalp cooling to be effective in preventing hair loss in patients with breast cancer who were receiving standard chemotherapy. There were 131 patients enrolled and 102 were found to have successful hair preservation. Minimal adverse effects were noted (3).

A Norwegian observational study was conducted. 54 patients with breast cancer received scalp cooling using the Paxman scalp cooling device. It was found that only 8% of these patients experienced significant hair loss. In addition, 89% of the patients described scalp cooling as acceptable with only minimal discomfort (9).

Massey (2004) conducted an observational study in the UK from 1997-2000. 95 patients with breast cancer were evaluated. There was a reported 89% success rate with the use of the Paxman scalp cooling device. 85% of the patients noted that during scalp cooling they were either "very comfortable", "reasonably comfortable" or "comfortable" (10).

References

a. Authors: Nangia, J., Wang, T., Osborne, C., Niraveth, P., Otte, K., Papish, S., Holmes, F., Abraham, J., Lacouture, M., Coutright, J>, Paxman, R., Rude, M., Hilsenbeck, S., Osborne, C., Rimawi, M.. Title: Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: the SCALP randomized clinical trial. Publication: JAMA Publication date: 2017; Issue: JAMA 317(6):Page/Line: 596-605. doi: 10.1001/jama.2016.20939.

b. Authors: Vasconcelos, I., Wiesske, A., Schoenegg, W.. Title: Scalp cooling successfully prevents alopecia in breast cancer patients undergoing anthracycline/taxane-based chemotherapy. Publication: The Breast Publication date: 2018; Issue: The Breast 40:Page/Line: 1-3. doi: 10.1016/j.breast.2018.04.012.

c. Authors: De Vries NF and Anderson OK. Title: Scalp cooling as a method of avoiding alopecia in cancer patients receiving chemotherapy. Publication: Presented at ECCO 11 Lisbon Publication date: 2011; Issue: Presented at ECCO 11 Lisbon:

d. Authors: Massey CS. Title: A multi-centre study to determine the efficacy and patient acceptability of the Paxman scalp cooling system to prevent hair loss in

patients receiving chemotherapy. Publication: Eur J Oncol Nursing Publication date: 2004; Issue: Eur J Oncol Nursing 8:Page/Line: 121-30.

3 - Rationale/Significance

3.1 Problem Statement

The problem statement will define the current knowledge of the problem of alopecia in this population. Alopecia can be a distressing and unwanted symptom experienced by patients with pancreatic cancer receiving nab-paclitaxel based regimens. In the IMPACT phase III registration trial of nab-paclitaxel plus gemcitabine given weekly x 3 q 4 weeks, a 50% rate of alopecia was observed (11). In a phase IB/II trial of 24 patients receiving nab-paclitaxel, gemcitabine plus cisplatin weekly x 2 q 3 weeks, grade 2 alopecia was noted in 100% of patients at the end of 3 cycles, per personal correspondence with principal investigator (12).

References

a. Authors: Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al.. Title: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. Publication: N Engl J Med Issue: N Engl J Med 2013; 369(18):Page/Line: 1691-1703. doi: 10.1056/NEJMoa1304369.

b. Authors: Jameson GS, Borazanci EH, Babiker HM, Poplin E, Niewiarowska A, Gordon M, Barrett MT, Ansaldo K, Lebron L, Stoll-D'Astice A, Rosenthal A, Shemanski L, Korn R, Ramanathan RK, Von Hoff DD. Title: A phase Ib/II pilot with nab-paclitaxel+gemcitabine+cisplatin in patients (pts) with Stage IV pancreatic cancer. Publication: American Society of Clinical Oncology (ASCO)-GI Conference Publication date: January 2017; Issue: American Society of Clinical Oncology (ASCO)-GI Conference:

3.2 Purpose of Study/Potential Impact

The purpose of the study is to determine the effectiveness of scalp cooling, using the FDA cleared Paxman scalp cooling device, in preventing alopecia in patients with pancreatic cancer undergoing treatment containing nab-paclitaxel, gemcitabine and cisplatin.

3.3.1 Potential Risks

According to the National Cancer Institute, it is estimated that over 56,000 new cases of pancreatic cancer will be diagnosed in 2019. In patients with pancreatic cancer, scalp metastasis is extremely rare and as of April 2019, there are very few reports in the literature. In 2013, Bdeiri and Kamar reported a patient with pancreatic cancer who presented with scalp metastasis. Their review of the literature revealed only 4 other reported similar cases (6).

Lemieux et al (2009) conducted a retrospective study of 640 patients with breast cancer. 553 of these patients used scalp cooling. The follow up time for those using scalp cooling was 5.8 years compared to 5.4 years for the control group. In the scalp cooling group, there was

a 1.1% reported incidence of scalp metastases compared to the 1.2% reported incidence in the control group (4).

Van den Hurk et al (2013) conducted a systemic review of 12 studies and the Munich Cancer Registry. 6,035 of the 48,711 patients with breast cancer used scalp cooling. Follow up was 2.2-9 years for the scalp cooling group compared to the 3-9.2 years for the control group. The scalp cooling group had a reported incidence of scalp metastases of 0.04%-1% compared to the control group with a 0.3%-3% reported incidence (5).

There can be adverse effects related to scalp cooling. The anticipated adverse effects are the following: chills, dizziness, headache, nausea, paresthesia, pruritus, sinus pain, skin and subcutaneous tissue disorders and skin ulceration(7).

Due to 2 out of 4 study participants reporting a headache during scalp cooling, patients will be offered a premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically appropriate by the provider.

References

a. Authors: Bdeiri, Kassem & Kamar, Francois. Title: Cutaneous metastasis of pancreatic adenocarcinoma as a first clinical manifestation: A case report and review of the literature. Publication: Gastrointestinal Cancer Research Publication date: 2013; Issue: March/April 2013:Page/Line: 61-63.

b. Authors: Lemieux, J., Amireault, C., Provencher, L., & Maunsell, E.. Title: Incidence of scalp metastases in breast cancer. A retrospective cohort study in women who were offered scalp cooling. Publication: Breast cancer treatment and research Publication date: 2009; Issue: Breast cancer treatment and research 118:Page/Line: 547-552. doi: 10.1007/s10549-009-0342-0.

c. Authors: van den Hurk, C.J., van de Poll-Franse, L.V., Breed, W.P., Coebergh, J.W., & Nortier, J.W.. Title: Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer. Publication: Breast Publication date: 2013; Issue: The Breast 22:Page/Line: 1001-1004. doi: 10.1016/j.breast.2013.07.039.

d. Authors: Paxman Coolers Limited. Title: The Paxman scalp cooler: instructions for use. Publication date: February 2018;

3.3.2 Potential Benefits

Hair preservation is the intended benefit to the patient.

At the end of the study, patients will be provided with an opportunity to continue scalp cooling at no cost. The patient will also be able to keep the cooling cap, at no cost.

4 - Study Objectives

4.1 Hypothesis

Patients with pancreatic cancer who are receiving treatment containing nab-paclitaxel, gemcitabine and cisplatin will experience hair preservation with the use of the Paxman scalp cooling device, at the end of three, 3 week cycles of chemotherapy.

4.2 Primary Objective

At the end of three, 3 week cycles of chemotherapy, patients will experience hair preservation defined as grade 0 or 1 alopecia, versus grade 2, as defined by CTCAE Version 5.0.

4.3 Secondary Objectives (if applicable)

To determine patient comfort while receiving scalp cooling, using the Paxman scalp cooling device, by asking one Likert scale question.

To determine reasons for patient report of "uncomfortable" or "very uncomfortable" during the scalp cooling period asking one qualitative question.

To identify chemotherapy-induced alopecia distress by utilizing the Chemotherapy-Induced Alopecia Distress Scale (CADS). The CADS instrument is a valid and reliable tool for measuring distress of chemotherapy-induced alopecia. The total score is calculated by summing the response for all items. The higher the score, the more distress related to chemotherapy-induced alopecia. Excellent internal consistency, indicating reliability, was found with Cronbach's alpha coefficient =0.95 for the total. The findings were similar with the validation dataset, showing external validity (1).

References

a. Authors: Cho, J., Choi, IR., Kim, YH., Im, YH., Park, S., Lee, S., Lee, JH., Yang, SJ. Title: Development and validation of Chemotherapy-Induced alopecia distress scale (CADS) for breast cancer patients. Publication: Annals of Oncology Publication date: 2014; Issue: 25(2):Page/Line: 346-351. doi: 10.1093/annonc.mdt476.

5 - Study Design

5.1 General Design Description

Pilot, feasibility study where patients will be selected using a convenience sample.

5.1.1 Study Date Range and Duration

The study is planned to start in August 2019 and run for 9 months.

5.1.2 Number of Study Sites

One study site

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary efficacy end points are successful hair preservation assessed using the Common Terminology Criteria for adverse events version 5.0 at the end of three cycles of chemotherapy.

5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

Secondary endpoints include reported comfort during scalp cooling and scores on Chemotherapy-Induced Alopecia Distress Scale (CADS).

5.3 Study Population

Adult patients with pancreatic cancer receiving a regimen containing nab-paclitaxel, gemcitabine and cisplatin

5.3.1 Number of Participants

Up to 15 patients with 10 evaluable after 3 cycles of treatment.

5.3.2 Eligibility Criteria/Vulnerable Populations

Patients with pancreatic cancer who are receiving a regimen containing nab-paclitaxel, gemcitabine and cisplatin will be included.

Inclusion Criteria:

- Willing and able to provide written informed consent/assent for the trial
- ≥18 years of age on day of signing informed consent
- Diagnosis of pancreatic cancer and scheduled to receive treatment with a regimen containing nab-paclitaxel, gemcitabine and cisplatin

Exclusion Criteria:

- Grade 1 alopecia
- Existing history of scalp metastases or the presence of scalp metastases is suspected
- CNS malignancies (either primary or metastatic)

- Cold sensitivity, cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia, cold migraine, cold urticaria, post-traumatic cold dystrophy
- Imminent bone marrow ablation chemotherapy
- Imminent skull radiation
- Previously received or scheduled to undergo skull irradiation
- Severe liver or renal disease from any etiology as patient may not be able to metabolize or clear the metabolites of the chemotherapeutic agent
- Skin cancers including melanoma, squamous cell carcinoma and Merkel cell carcinoma
- Small cell carcinoma of the lung
- Solid tumors that have a high likelihood for metastasis in transit
- Squamous cell carcinoma of the lung

6 - Methods

6.1 Treatment - Device

6.1.1 Intended use for the device

The Paxman Scalp Cooling device has been FDA cleared for use in patients with solid tumors.

6.1.2 Device administration and schedule

Patients will undergo scalp cooling via the Paxman Scalp Cooling device for the first 3 cycles of treatment. Cooling will consist of precooling (30 minutes); infusion cooling (will vary depending upon the length of time to infuse the chemotherapy) and post infusion cooling (90 minutes).

Screening Visit

- Occurs less than or equal to 10 days prior to C1D1 of the nab-paclitaxel, gemcitabine and cisplatin therapy
- Review of inclusion/exclusion criteria
- Signing informed consent
- Fitting for the scalp cooling cap
- Photographs of the top of head, back of head, right and left sides of head

C1D1

- Review of inclusion/exclusion criteria
- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events (grade 3 or higher related or possibly related to scalp cooling) following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C1D8

- Scalp Cooling
- Adverse events (grade 3 or higher related or possibly related to scalp cooling) following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C2D1

- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events (grade 3 or higher related or possibly related to scalp cooling) following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C2D8

- Scalp Cooling
- Adverse events (grade 3 or higher related or possibly related to scalp cooling) following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C3D1

- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events (grade 3 or higher related or possibly related to scalp cooling) following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C3D8

- Scalp Cooling
- Adverse events (grade 3 or higher related or possibly related to scalp cooling) following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

End of Study

- 2-3 weeks after last chemotherapy treatment in Cycle 3
- Photographs of the top of head, back of head, right and left sides of head
- Subject questionnaire-CADS

It is important to note that the principal investigator will conduct training with specific staff on how to take the photographs required for this study. A training log will be kept. The same camera and background will be used for all photographs. In addition, the patient will use a blank sheet of white paper (8.5x11") to cover the face. A photograph will be taken of the top of the head, back of the head, right side and left side at various time points during the study. The patient will be asked to use a blank sheet of white paper (8.5x11") to cover the face. The study Sponsor may use the photos at medical meetings and in medical magazines, so that others can find out about the study. The patient will not be identified by name or other identifying information from the photo in any such publications. The patient will be asked to sign a separate form consenting to the photographs as the photographs are a mandatory

part of the study. The photographs will be kept in a password protected electronic file on the oraganizations server and accessible only to study team members for a period of 7 years.

A representative from Paxman will train specific staff on how to fit patients for the cooling cap. A training log will be kept.

6.1.3 Method of Assignment/Randomization

N/A

6.1.4 Device Calibration

The Paxman scalp cooling device is calibrated prior to delivery and then serviced every two years by Paxman.

6.1.5 Storage Condition

The Paxman scalp cooling device is required to be stored in a space that is dry and clean.

6.1.6 Concomittant therapy

There are no restrictions related to concomitant therapy. Patients will be offered premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider. This will be based upon clinical factors and patient co-morbidities.

6.1.7 Restrictions

There are no restrictions.

6.2 Assessments

6.2.1 Efficacy

Hair loss will be assessed using CTCAE version 5.0 guidelines on C1D1 (prior to treatment), on C2D1 (prior to treatment), C3D1 (prior to treatment) and then at End of Study. Photographs will also be collected on these days (top of head, back, right side and left side). Adverse events related or possibly related to scalp cooling, grade 3 or higher, as guided by the CTCAE version 5.0 guidelines, will be collected at the end of every cooling cap treatment in addition to patient reported comfort.

6.2.2 Safety/Pregnancy-related policy

All patients who are receiving chemotherapy are counseled to prevent pregnancy. If a pregnancy is noted during the study, the pregnancy will be reported.

6.2.2.1 Adverse Events Definition and Reporting

Adverse Events related or possibly related to scalp cooling, grade 3 of higher, will be collected at the end of every cooling cap treatment. The investigator should follow AEs/SAEs

observed during the study until they resolve or stabilize, the patient is lost to follow-up, of the events are otherwise explained.

An investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP website at :

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

When specific adverse events are not listed in the CTCAE they will be graded by the investigator according to the following grades and definitions, consistent with the CTCAE Version 5.0

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

- Grade 4: Life-threating consequences; urgent intervention indicated

- Grade 5: Death related to AE

6.2.3 Pharmacokinetics (if applicable)

N/A

6.2.4 Biomarkers (if applicable)

N/A

6.3 Study Procedures

6.3.1 Study Schedule

The Visit Schedule Table in the Appendix summarizes the procedures to be performed at each visit.

Patients will undergo scalp cooling via the Paxman Scalp Cooling device for the first 3 cycles of treatment. Cooling will consist of precooling (30 minutes); infusion cooling (will vary depending upon the length of time to infuse the chemotherapy) and post infusion cooling (90 minutes).

The dose and schedule of nab-paclitaxel will also be collected through Cycle 3 (dose modification and/or missed doses can impact hair loss and regrowth).

Screening Visit

- Occurs less than or equal to 10 days prior to C1D1 of a regimen consisting of nab-paclitaxel, gemcitabine and cisplatin therapy
- Review of inclusion/exclusion criteria
- Signing informed consent
- Fitting for the scalp cooling cap
- Photographs of the top of head, back of head, right and left sides of head

C1D1

- Review of inclusion/exclusion criteria
- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C1D8

- Scalp Cooling

- Adverse events, grade 3 or higher related or possibly related to scalp cooling following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C2D1

- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C2D8

- Scalp Cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C3D1

- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling

- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C3D8

- Scalp Cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

End of Study

- 2-3 weeks after last chemotherapy treatment in Cycle 3
- Photographs of the top of head, back of head, right and left sides of head
- Subject questionnaire-CADS

6.3.2 Informed Consent

The Investigator must obtain documented consent from each potential patient prior to participating in a clinical trial.

Consent must be documented by the patient's dated signature. A copy of the signed and dated consent form should be given to the patient before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to

the patient's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the patient's dated signature.

The informed consent will adhere to the IRB requirements, applicable laws and regulations.

6.3.3 Screening

The Investigator or qualified designee will perform screening procedures, including review of inclusion/exclusion criteria.

The Investigator or qualified designee will take baseline photographs (top of head, back of head, right side, and left side).

The Investigator or qualified designee will also measure the patient to determine the appropriate size of the cooling cap.

6.3.4 Recruitment, Enrollment and Retention

Patients who are going to receive a regimen containing nab-paclitaxel, gemcitabine and cisplatin will be notified of this study by the investigator or designee.

6.3.5 On Study Visits

Patients will undergo scalp cooling via the Paxman Scalp Cooling device for the first 3 cycles of treatment. Cooling will consist of precooling (30 minutes); infusion cooling (will vary depending upon the length of time to infuse the chemotherapy) and post infusion cooling (90 minutes).

The dose and schedule of nab-paclitaxel will also be collected through Cycle 3 (dose modification and/or missed doses can impact hair loss and regrowth).

Screening Visit

- Occurs less than or equal to 10 days prior to C1D1 of the nab-paclitaxel, gemcitabine and cisplatin therapy
- Review of inclusion/exclusion criteria
- Signing informed consent
- Fitting for the scalp cooling cap
- Photographs of the top of head, back of head, right and left sides of head

C1D1

- Review of inclusion/exclusion criteria
- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS

- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C1D8

- Scalp Cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C2D1

- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C2D8

- Scalp Cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling

- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C3D1

- Photographs of the top of head, back of head, right and left sides of head prior to scalp cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire prior to scalp cooling-CADS
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Scalp Cooling
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

C3D8

- Scalp Cooling
- Adverse events, grade 3 or higher related or possibly related to scalp cooling, following scalp cooling
- Subject questionnaire following scalp cooling-Comfort asking one Likert-style question and then asking patient reason if they were "uncomfortable" or "very uncomfortable" during the treatment
- Offer premedication of Tylenol 650mg or Ibuprofen 400mg if deemed clinically safe by the provider

6.3.6 End of Study and Follow-up

End of Study

- 2-3 weeks after last chemotherapy treatment in Cycle 3
- Photographs of the top of head, back of head, right and left sides of head

- Subject questionnaire-CADS

6.3.7 Removal of subjects

Patients may withdraw at any time from this study.

6.4 Statistical Method

6.4.1 Statistical Design

This is a pilot, feasibility study using a convenience sample.

Descriptive statistics including demographics will be calculated for the sample.

All data will be screening for parametric and non-parametric statistical test assumptions. Data will be entered and analyzed in IBM SPSS version 25. The pilot will be considered a success if ≥ 30% of the participants have grade 0 or 1 alopecia at the end of the study as grade 2 alopecia has been seen in 100% of the patients receiving the combination of Nab-paclitaxel, gemcitabine and cisplatin.

The primary endpoint is hair preservation defined as grade 0 or 1 alopecia as defined by CTCAE Version 5.0 at the end of three cycles of chemotherapy.

6.4.2 Sample Size Considerations

The sample size of this pilot study will be up to 15 patients with 10 evaluable after 3 cycles of treatment.

This study utilizes a convenience sample. Accordingly, the sample size for this investigation is not statistically based.

6.4.3 Planned Analyses

6.4.3.1 Primary Analyses

The response for each patient will be measured on Day 1 of Cycles 1, 2 and 3 and then again at the End of Study Visit.

Hair preservation is defined as grade 0 or 1 alopecia as defined by CTCAE Version 5.0

A one arm, repeated measures design will be employed to assess hair loss in each patient from baseline to post-treatment with the goal of hair preservation.

The response of the patients will be compared to a historic control where it is known that 100% of patients receiving this regimen who do not use scalp cooling will experience grade 2 alopecia.

6.4.3.2 Secondary Objectives Analyses

Secondary objective analyses will include the following:

Descriptive statistics (means and standard deviations) will be calculated on patient comfort while receiving scalp cooling (Likert type scale) and chemotherapy induced alopecia distress (the higher the score, the higher the distress).

6.4.3.3 Safety/Pregnancy-related policy

All patients who are receiving chemotherapy are counseled to prevent pregnancy. If a pregnancy is noted during the study, the pregnancy will be reported.

6.4.3.4 Analysis of Subject Characteristics

The following demographic data will be collected for each patient:

Age

Gender

Race

Ethnicity

Date of Cancer Diagnosis

6.4.3.5 Interim Analysis (if applicable)

N/A

6.4.3.6 Health economic evaluation

N/A

6.4.3.7 Other

N/A

6.4.4 Subsets and Covariates

N/A

6.4.5 Handling of Missing Data

N/A

7 - Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, patient diaries, patient questionnaires/surveys, if applicable, from the IRB. All correspondence with the IRB should be retained in the investigator file.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per the IRB's policies.

7.3 Subject Confidentiality

The Investigator and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other information (hereinafter collectively "information") disclosed to the Investigator or other study personnel. Such information shall remain the confidential and proprietary property of HonorHealth, and shall be disclosed only to the Investigator or other designated study personnel.

The obligation of non-disclosure shall not apply to the following:

- relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- information after such time that it is or becomes publicly available through no fault of the Investigator or other study personnel; and,
- information after such time that it is disclosed to the Investigator by a third party entitled to disclose such information.

If the study site is a 'covered site' under the definitions of the Health Insurance Portability and Accounting Act (HIPAA), the Investigator will ensure that the patient consents to the use of data by HonorHealth and its designees for the purposes of regulatory submissions, study publications, and drug approval.

7.4 Deviations/Unanticipated Problems

If the study team becomes aware of an anticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB.

7.5 Data Collection

Data collection is the responsibility of the clinical staff at the site under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study.

7.6 Data Quality Assurance

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

7.7 Study Records

Source documents serve as the evidence of the existence of the patient and the data collected for this trial. Source documents will be the responsibility of the Investigator and will be filed at the site and available as needed for 7 years following the completion of the study.

7.8 Access to Source

N/A

7.9 Data or Specimen Storage/Security

Data will be kept in a password-protected electronic file on the organization's server and accessible only to study team members. Findings will be presented in summary format. No personal health information will be disclosed. Only key personnel will have access to the data.

7.10 Retention of Records

Study documents will be retained 7 years following the completion of the study. Documents will be retained for a longer period, if required by local regulations.

7.11 Study Monitoring

Data monitoring procedures will be carried out by the site and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

7.12 Data Safety Monitoring Plan

An external data safety monitoring committee will not be established for this study.

7.13 Study Modification

Any study modifications will be submitted to the IRB for approval prior to implementation.

7.14 Study Discontinuation

N/A

7.15 Study Completion

N/A

7.16 Conflict of Interest Policy

Conflict of interest documentation will be provided to the IRB along with the protocol submission.

7.17 Funding Source

The study will be funded by the Dr. Jill Gives Hope Foundation.

7.18 Publication Plan

Within one year of study completion, a manuscript will be prepared and submitted to a peer reviewed journal.

Appendices

Appendix #	Title	Section	Topic
1	Schedule of Events	6 Methods	6.1.2 Device administration and schedule

List of Tables

References

1. Cho, J., Choi, IR., Kim, YH., Im, YH., Park, S., Lee, S., Lee, JH., Yang, SJ. Development and validation of Chemotherapy-Induced alopecia distress scale (CADS) for breast cancer patients. Annals of Oncology 2014; 25(2):346-351. doi: 10.1093/annonc.mdt476.

2. Nangia, J., Wang, T., Osborne, C., Niraveth, P., Otte, K., Papish, S., Holmes, F., Abraham, J., Lacouture, M., Coutright, J>, Paxman, R., Rude, M., Hilsenbeck, S., Osborne, C., Rimawi, M.. Effect of a scalp cooling device on alopecia in women undergoing chemotherapy for breast cancer: the SCALP randomized clinical trial. JAMA 2017; JAMA 317(6):596-605. doi: 10.1001/jama.2016.20939.

3. Vasconcelos, I., Wiesske, A., Schoenegg, W.. Scalp cooling successfully prevents alopecia in breast cancer patients undergoing anthracycline/taxane-based chemotherapy. The Breast 2018; The Breast 40:1-3. doi: 10.1016/j.breast.2018.04.012.

4. Lemieux, J., Amireault, C., Provencher, L., & Maunsell, E.. Incidence of scalp metastases in breast cancer. A retrospective cohort study in women who were offered scalp cooling. Breast cancer treatment and research 2009; Breast cancer treatment and research 118:547-552. doi: 10.1007/s10549-009-0342-0.

5. van den Hurk, C.J., van de Poll-Franse, L.V., Breed, W.P., Coebergh, J.W., & Nortier, J.W.. Scalp cooling to prevent alopecia after chemotherapy can be considered safe in patients with breast cancer. Breast 2013; The Breast 22:1001-1004. doi: 10.1016/j.breast.2013.07.039.

6. Bdeiri, Kassem & Kamar, Francois. Cutaneous metastasis of pancreatic adenocarcinoma as a first clinical manifestation: A case report and review of the literature. Gastrointestinal Cancer Research 2013; March/April 2013:61-63.

7. Paxman Coolers Limited. The Paxman scalp cooler: instructions for use. February 2018;

8. Betticher, D.C., Delmore, G., Breitenstein, U., Anchisi, S., Zimmerli-Shwab, B., Muller, A., ...Trueb, R.R.. Efficacy and tolerability of two scalp cooling systems for the prevention of alopecia associated with docetaxel treatment. Supportive Care in Cancer 2013; 21:2565-2573. doi: 10.1007/s00520-013-1804-9.

9. De Vries NF and Anderson OK. Scalp cooling as a method of avoiding alopecia in cancer patients receiving chemotherapy. Presented at ECCO 11 Lisbon 2011; Presented at ECCO 11 Lisbon:

10. Massey CS. A multi-centre study to determine the efficacy and patient acceptability of the Paxman scalp cooling system to prevent hair loss in patients receiving chemotherapy. Eur J Oncol Nursing 2004; Eur J Oncol Nursing 8:121-30.

11. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al.. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med N Engl J Med 2013; 369(18):1691-1703. doi: 10.1056/NEJMoa1304369.

12. Jameson GS, Borazanci EH, Babiker HM, Poplin E, Niewiarowska A, Gordon M, Barrett MT, Ansaldo K, Lebron L, Stoll-D'Astice A, Rosenthal A, Shemanski L, Korn R, Ramanathan RK, Von Hoff DD. A phase Ib/II pilot with nab-paclitaxel+gemcitabine+cisplatin in patients (pts) with Stage IV pancreatic cancer. American Society of Clinical Oncology (ASCO)-GI Conference January 2017; American Society of Clinical Oncology (ASCO)-GI Conference: