TITLE: *Effect of Artificial Tears on Radioiodine Levels in the Nasolacrimal Duct System of Patients Following Radioiodine Therapy for Thyroid Carcinoma*

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 *To assess whether use of preservative free artificial tears following radioactive iodine administration will lower the level of radioactive iodine in the tears of patients treated with radioactive iodine for thyroid carcinoma.*

1.2 Secondary Objectives

1.2.1 *Secondary objective is to deduce whether artificial tears would be an effective preventative intervention to decrease the risk of developing nasolacrimal duct stenosis, which has been associated with radioactive iodine administration. Patients will be monitored over time for development of nasolacrimal duct stenosis symptoms, such as epiphora or tear duct infections.*

2. BACKGROUND

2.1 Study Disease(s)

Radioactive iodine is commonly used for the treatment of thyroid carcinoma. The association of radioiodine therapy for the treatment of differential thyroid carcinoma with nasolacrimal duct dysfunction has been well documented in many research studies.[1–3] *Doses of 150 mCi or more, which are frequently used in the treatment of thyroid carcinoma, have been found to significantly increase a patient's risk of developing nasolacrimal duct obstruction.*[2,4,5] *Prior studies have estimated the incidence of radioactive iodine associated nasolacrimal duct obstruction to be around 3 to 4.6%.*[2,6]

Prior case reports have documented radioactive iodine detection in the tears of patients following radioiodine ablation for thyroid cancer.[7,8] *A likely mechanism is that the radioactive iodine is taken up from the tears by the stratified columnar epithelial cells of the lacrimal sac and nasolacrimal ducts, leading to inflammation and fibrosis, and subsequent stenosis and obstruction of the lacrimal lumen over time.*[9]

The purpose of this study is to explore whether administration of preservative free artificial tears will decrease the level of detectable radioiodine in the tears and nasolacrimal duct system of patients undergoing radioiodine therapy for differential thyroid carcinoma. There are no current studies analyzing what threshold of radioactive iodine in tears is considered to be less likely to cause nasolacrimal duct stenosis. Given that radioactive iodine uptake by the epithelial cells lining the lacrimal sac is the likely cause of subsequent fibrosis and obstruction, the hypothesis is that decreasing the concentration of radioactive iodine in tears as much as

possible with artificial tears will thus decrease the risk of developing nasolacrimal duct obstruction. We believe that the lower the radioactive iodine level in tears, the lower the risk of developing nasolacrimal duct obstruction.

We will recruit a total of 5 patients who wear bilateral disposable contact lenses, have them self-administer preservative free artificial tears in the right contact-wearing eye (left contact-wearing eye will receive no tears), and obtain their tear-containing contact lenses from both eyes and measure radioiodine levels.

3. PATIENT SELECTION

3.1 Eligibility Criteria

There will be no age restriction to this study.
Inclusion Criteria (must meet all below to be recruited):

1. *Radio-iodine therapy for thyroid cancer*
2. *Radioiodine therapy ≥150mCi*
3. *Patient wears contacts on both eyes*

3.2 Exclusion Criteria

Exclusion Criteria:

1. *Use of eye drops, other than artificial tears*
2. *History of ocular/lacrimal gland trauma*
3. *History of lacrimal drainage disease: canaliculitis, dacryocystitis*
4. *Prior radiotherapy*
5. *Current or prior use of chemotherapy drugs (i.e. 5-fluorouracil, docetaxel)*
6. *Medical conditions that predispose to NLD stenosis*
    a. *Sarcoid*
    b. *Granulomatosis with polyangiitis*
    c. *Chronic lymphocytic leukemia*

4. REGISTRATION PROCEDURES

Patients will be identified through the Nuclear Medicine and/or Endocrine department. Patients who meet all inclusion criteria will be asked whether they would like to participate in the study.

5. TREATMENT AND/OR IMAGING PLAN

5.1 Agent Administration

Artificial tears are the study agent of interest and bear minimal risks and side effects. The regimen for self-administration of artificial tears is as follows: on Day 1, patients will self-administer artificial tears every 15 minutes for 2 hours followed by every 30 minutes for 4 hours. On Day 2, patients will self-administer artificial tears every 1 hour for 12 hours. On Day 3, patients will self-administer artificial tears four times that day. On Day 4, patients will self-administer tears twice that day. Patients will be instructed to wear their contact lenses throughout their waking hours. The rationale for this proposed regimen is to dilute the radioactive iodine from the tear ducts with frequent administration of artificial tears. Zettinig et al showed that radioiodine levels are highest in tears on the first day and significantly decrease over 4-5 days,[8] *which serves as the underlying rationale for having patients self-administer artificial tears for four days.*

Routine whole body scintigraphy (WBS) and/or single photon emission computed tomography (SPECT-CT) will be obtained around 1 week post-radioiodine as part of the routine care patients receive after having radioiodine administration for treatment of thyroid cancer. No adjustments will be made to this routine imaging that patients receive. We will analyze the routine images for localization of radioiodine in the intranasal and nasolacrimal duct regions.

5.1.1 Primary and Secondary Endpoint

The primary endpoint will be to assess for the development of nasolacrimal duct obstruction over two years in 8 month intervals. Every 8 months, each patient will be assessed in the ophthalmology clinic for nasolacrimal duct dysfunction via tear duct irrigation. The secondary endpoint is the level of radioactive iodine measured in the tears of patients collected via their contact lenses. Patients will be asked to store their daily contact lenses in sterile container for subsequent radioactive iodine level analysis via a well counter in the Nuclear Medicine department. These contact lenses will be collected at their 1 week routine appointment with Nuclear Medicine.

5.1.2 Other Modality(ies) or Procedures

Patients' tears will be collected through contact lenses (4 days worth from both eyes of each patient), which will be stored in unused contact lens containers daily and subsequently collected during routine 1 week follow-up appointments with Nuclear Medicine. The lenses will be analyzed for radioactive iodine levels. Routine post-radioiodine imaging (single-photon emission computed tomography and/or whole body scintigraphy) will be obtained to assess for radioactivity in the nasolacrimal or intranasal region.

6. STATISTICAL CONSIDERATIONS

Radioactive iodine levels from the right contact lenses of patients will be compared to that of the left contact lenses that did not have exposure to artificial tears. The data gathered will be analyzed by the statistics personnel in the department of Ophthalmology.

In more detail: the area under the curve (AUC) of all four days for each patient was calculated as the sum of the four trapezoid areas under the I-131 exposure values. To meet the normality assumption, I-131 activities and AUCs were logarithmically transformed to obtain geometric mean I-131 activities of each day and geometric mean AUCs. The Shapiro-Wilk test was used to evaluate the normal assumption for logarithmically transformed AUCs (log-AUCs). The 95% confidence intervals (CI) of the AUCs were constructed for the right experimental eyes and left control eyes, assuming normality for log-AUCs, which were compared between the two groups using paired t-tests. Statistical analyses were conducted using R version 4.1.2 (R Project for Statistical Computing, www.r-project.org). Two sided $p<0.05$ was considered statistically significant.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Preservative- free artificial tears have rare side effects. Because they are preservative free, there is minimal harm to the cornea. Possible side effects include watery eyes, possible allergic reaction, eye irritation not present before use of the artificial tears, or possible blurry vision. Persistent irritation of the eyes is an indication for stopping artificial tears. These side effects will likely end with discontinuation of the artificial tears and are unlikely to have long-term sequela.

There have been no studies conducted regarding the dose delay or dose reduction of artificial tears. It is possible that increasing the frequency of administration of artificial tears may increase the risk of developing the above possible side effects.

8. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.
The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

9. REFERENCES

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