

**Basal Cell Carcinoma
Chemoprophylaxis with Tazarotene:
A Randomized, Double-Blind,
Placebo-Controlled
Clinical Trial**

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1. Study Purpose and Rationale

Basal Cell Carcinoma (BCC) is the most common malignancy in human beings. Its annual incidence in the United States is 900,000 cases. Estimated lifetime risk for Caucasian American women is between twenty-three and twenty-eight percent, while the risk for American men is between thirty-three and thirty-nine percent. BCC does not cause significant mortality, however it can cause considerable morbidity. For example, if allowed to grow large, and depending on where on the body the BCC occurs, surgical removal of BCCs can result in disfigurement. The tumors can also invade nerve tissue, impairing nerve function and, at times, causing blindness. Furthermore, if a tumor grows rapidly it can ulcerate and serve as a nidus for infection.

The current treatment for BCC is surgical excision. There is no medical treatment at this time. There have been promising studies documenting a reduction in number of BCCs with oral retinoid therapy. Unfortunately, the dose necessary to produce an effect is large and accompanied by panoply of side effects that most patients find intolerable.

The success of oral retinoid therapy in the prevention of BCC, and the accompanying side effects beg the question: can topical retinoids achieve the same reduction in number of BCCs without the high systemic levels and side effects?

There is some peripheral evidence that topical retinoids do indeed inhibit the development of BCC. However, there has not been a gold standard randomized, double-blind, placebo-controlled clinical trial to provide definitive evidence on the relationship between topical retinoids and BCC.

The study we propose asks: If a retinoid cream is applied daily, can it reduce the occurrence of BCC?

The particular retinoid we wish to study is Tazarotene, a retinoid with relative specificity for RAR- β and RAR- γ receptors. Tazarotene is currently marketed as a topical treatment for psoriasis and acne. However, while treating psoriasis and acne, there have been incidental findings of a reduction in BCC occurrence.

2. Review of the Literature

In one open-label study, sixteen of thirty sporadic BCCs *disappeared* after treatment with tazarotene for up to eight monthsⁱⁱⁱ. This study, with over 100 patients, suggested an approximately 50% cure rateⁱⁱⁱ.

There have also been mouse studies that examined the role of topical tazarotene in BCC chemoprevention. One study looked at Ptch1+/1 mice, a simulation of the genetic mutation responsible for Basal Cell Nevus Syndrome. In this study tumors were induced with ionizing radiation or ultraviolet radiation. These studies found that tazarotene causes an approximately 85% reduction in number and size of microscopic tumors (identified in skin biopsy), as well as a near total prevention of macroscopic BCCs^{iv}.

3. Hypothesis

Tazarotene cream inhibits growth of BCC, therefore daily application of Tazarotene cream may prevent the development of BCC. We would like to test the safety and efficacy of tazarotene 0.1% cream in the prevention of BCC.

4. Methods

Study Population

We will recruit patients with Basal Cell Nevus Syndrome (BCNS), a genetic disease that predisposes to BCC. These patients typically develop one to three BCC lesions per year. Patients of this population have been notified of a therapeutic trial, and those who contact us with a desire to participate in a trial will be considered.

Primary Outcome

Conceptual Definition:

A reduction in the number of BCCs for a given patient, as measured by physical exam every three months for three years, with biopsy confirmation
Reduction in number of BCCs \geq nine mm² per month during the two years on tazarotene when compared to the expected number of BCCs *for that patient*.

Operational Definition:

The determination of BCC occurrence will be based on physical exams conducted every three months for three years. The expected number of BCCs for a given patient will be based on the behavior of their disorder during the year on vehicle cream.

Secondary Outcomes

Secondary outcomes will consist of an exploration of the relationship between tazarotene cream and total BCC burden, where total BCC burden is defined as the sum of all lesion surface areas. We will also investigate the possibility of a carry-over or washout effect of the tazarotene cream.

Methods

We will recruit forty-two patients in total. Thirty-five will be randomized to receive vehicle cream during the first twelve months, followed by 0.1% tazarotene cream during the subsequent twenty-four months. Meanwhile, the remaining seven patients will be randomized to receive tazarotene cream during the initial year and vehicle for the subsequent twenty-four months. Tazarotene efficacy will only be evaluated in the group randomized to begin with vehicle. The purpose of the seven patients in the other arm is to maintain blindness and to study a potential carry-over effect.

Patients will have physical exams every three months for the thirty-six months of their trial participation. At these physical exams they will have both their back and chest examined. Tazarotene efficacy will be measured by the chest observations. The comparison of the number of BCCs observed on the chest during vehicle with the number of BCCs during tazarotene will determine the chemopreventive efficacy of tazarotene. We check the back in addition to the chest in order to account for period effect.

5. Study Design

This will be a prospective, longitudinal, interventional, randomized, vehicle-controlled, double-blind, multi-center crossover clinical trial.

6. Enrollment

We will recruit a total of forty-two subjects. Thirty-five of the forty-two will be randomized to placebo for months zero through twelve, followed by tazarotene for the subsequent twenty-four months. Seven subjects will be randomized to tazarotene for the first year and then vehicle for the remaining two years.

Total of 42 subjects:

✓ **35 subjects:**

- ✓ Months 0-12: placebo
- ✓ Months 13-37: tazarotene

✓ **7 subjects:**

- ✓ Months 0-12: tazarotene
- ✓ Months 13-37: placebo

7. Statistical Analysis

The null hypothesis is that the responders will be less than or equal to twenty percent of the arm two population (randomized to one year of vehicle followed by two years of tazarotene). The alternative hypothesis is that responders will make up greater than or equal to fifty percent of this population.

H₀: % responders ≤ 20%

H_A: % responders ≥ 50%

We will analyze the data using a random effects longitudinal analysis of total lesions over time. Comparison will be made within the same patient; we will *not* be comparing two randomized arms, as this would be confounded by carry-over effect. We will use a two-sided binomial exact test to analyze the primary outcome (the proportion of responders).

8. Sample Size & Power Analysis

Why did we choose a sample size of forty-two?

We need forty-two patients in order to demonstrate a statistically significant reduction in BCC incidence with tazarotene cream as compared to placebo. This is because we anticipate a thirty-percent attrition proportion, leaving twenty-four subjects in the crucial arm of the trial (recall: we are only evaluating tazarotene effectiveness in the arm randomized first to placebo, then to tazarotene). We need twenty-four subjects in arm two to be able to have eighty-four percent power, with a type I error of 4.2%, when we test the hypothesis:

H₀: %responders ≤ 20%

H_A: %responders ≥ 50%

We will reject the null hypothesis if greater than ten subjects respond to tazarotene.

- Reject H_0 if >10 subjects respond
- Type I error = 4.2%
- Power = 84%

9. Study Drugs

Patients will be instructed to apply cream to the chest and back once daily. The cream will be either 0.1% tazarotene cream, or vehicle cream. When patients return to study center for check-ups at three-month intervals, they will bring their used containers, and they will be given new bottles.

10. Study Questionnaires

Patients will fill out a screening questionnaire during their pre-registration, which will help us to discern those eligible for the study.

11. Subject Selection: Basal Cell Nevus Syndrome

Basal Cell Nevus Syndrome (BCNS) is a rare autosomal dominant disorder, which results in exquisite susceptibility to BCC in affected individuals. Patients typically develop tens to hundreds of BCCs over their lifetime.^v

Inclusion Criteria

- Basal Cell Nevus Syndrome
- At least three BCC's greater than or equal to nine mm² on both chest *and* back within the past year
 - o Must be diagnosed clinically by a study investigator and/or documented Histologically
- Eighteen to seventy-five years old
- If female and of child-bearing potential:
 - o Must have a negative serum β -hCG at the baseline evaluation
 - o Must not be lactating
 - o Must be using adequate contraception (oral contraception, IUD, sterilization, spermicidal gel with diaphragm or condom)

Exclusion Criteria

- Pregnancy
- Patient has used topical/systemic agents that may interfere with the evaluation:
 - Glucocorticoids
 - Retinoids
 - α -hydroxy acids
 - 5-FU
 - Systemic chemotherapy
- History of hypersensitivity to any of the ingredients in the treatment

- If patient is for any reason unable to return for follow-up
- If the patient has any health condition or situation that may put him or her at significant risk

12. Recruitment

Patients will be recruited among those who respond to notification of a therapeutic trial for Basal Cell Nevus Syndrome. From those who express interest, we will determine who meets inclusion criteria through a screening questionnaire and comprehensive examination of their medical records. Patients will be asked to sign a consent form during pre-registration allowing us to view their records. We will obtain informed consent from patients when we meet with them, first for pre-registration, and then again at the baseline interview.

13. Confidentiality of Study Data

Confidentiality will be protected using standard CUMC clinical protocol procedures outlined by the CUMC IRB and HIPAA.

14. Potential Risks

Tazarotene cream has been associated with mild side effects, predominantly local irritation. There is risk of teratogenicity, therefore we will ensure that all women of child-bearing potential are not pregnant or lactating and that they are using adequate contraception.

15. Potential Benefits

Subjects enrolled in this study have a rare genetic disorder that puts them at increased risk for development of BCC. By participating in this study, they may have earlier detection of their lesions, and they may have reduced rate of BCC development as a result of tazarotene treatment. Beyond the immediate benefits of the study, the knowledge we gain from this examination may help us establish a gold standard of treatment for prevention of BCC, which will benefit study participants as well as the general public.

16. Alternatives

Alternatives to participation in this study are to not use tazarotene, but to rely on previously established methods of BCC prevention, including avoiding excessive sun exposure and tanning booths, using spf protection, and hats and clothing to cover skin.

17. Follow-Up

BCC's will be removed by primary skin care physicians or at Study Centers.

18. Generalizability

BCNS is caused by a defective copy of *PTCH1*, which is a tumor suppressor gene.^{viii} *PTCH1* mutations with loss of wild-type alleles have been identified in sporadic BCCs.^{viiiixixii} These findings suggest a possible common genetic root for both hereditary and sporadic BCCs. We can therefore conclude that the results of our study could conceivably be generalizable to all those affected by BCC, not simply those with BCNS.

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