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Tazarotene: Randomized, Double-Blind, Vehicle-Controlled, and Open-Label Concurrent Trials for Basal Cell Carcinoma Prevention and Therapy in Patients with Basal Cell Nevus Syndrome

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Abstract

Sporadic human basal cell carcinomas (BCC) are generally well managed with current surgical modalities. However, in the subset of high-risk patients predisposed to developing large numbers of BCCs, there is an unmet need for effective, low-morbidity chemoprevention. This population includes fair-skinned patients with extensive sun exposure and those with genodermatoses such as the basal cell nevus (Gorlin) syndrome (BCNS). Tazarotene (Tazorac, Allergan) is a topical retinoid with relative specificity for RAR-β and RAR-γ receptors. We previously demonstrated tazarotene's robust anti-BCC efficacy in Ptch1$^{+/-}$ mice, a murine equivalent of BCNS, and others have found it to have some efficacy against sporadic human BCCs. We report here results of a randomized, double-blind, vehicle-controlled study in patients with BCNS evaluating the efficacy of topically applied tazarotene for BCC chemoprevention ($N = 34$ subjects), along with an open-label trial evaluating tazarotene's efficacy for chemotherapy of BCC lesions ($N = 36$ subjects) for a maximum follow-up period of 3 years. We found that only 6% of patients had a chemopreventive response and that only 6% of treated BCC target lesions were clinically cured. Our studies provide no evidence for either chemopreventive or chemotherapeutic effect of tazarotene against BCCs in patients with BCNS. *Cancer Prev Res; 7(3); 292–9. ©2014 AACR.*

Introduction

Basal cell carcinoma (BCC) is a common malignancy that comprises 70% to 80% of the 2 to 3 million nonmelanoma skin cancers diagnosed annually in the United States (1, 2). For patients with a limited number of lesions, both simple excision and microscopically controlled surgery (Mohs) achieve excellent local control with 5-year recurrence rates of approximately 4% and 2%, respectively (3). Nevertheless, there are subsets of patients with a higher burden of BCCs for whom repeated surgical procedures are intolerable. These include fair-skinned patients with extensive sun exposure and those with certain genodermatoses (4). Patients with the autosomal-dominantly inherited basal cell nevus (Gorlin) syndrome (BCNS) are highly susceptible to BCC tumors, developing tens to hundreds of these lesions (5). Management of these patients is challenging, and management with oral retinoids or field therapy with topical 5-fluorouracil, topical imiquimod, photodynamic therapy, or carbon laser resurfacing have been attempted with limited success (6, 7). For these high-burden patients, development of more successful chemoprevention or nontoxic chemotherapy would deliver significant quality of life benefits.

Retinoids are the best-studied agents for BCC chemoprevention—oral retinoids can reduce the incidence of new BCC lesions in select high-risk populations. Thus, oral isotretinoin, acetretin, and etretinate can reduce BCCs in patients with xeroderma pigmentosum, immunosuppression after organ transplantation, and BCNS (8–13). However, oral retinoids cause significant side-effects at doses needed for anti-BCC efficacy, limiting their widespread adoption for chemoprevention. Oral α-difluoromethylomithine (DMFO), an inhibitor of ornithine decarboxylase, also has some BCC chemopreventive efficacy (14). In contrast, oral vismodegib, the first U.S. Food and Drug Administration approved small molecule inhibitor of the Hedgehog (HH) signaling pathway, reduced by 20-fold the development of BCCs in patients with BCNS but adverse events led half of patients to discontinue the drug at least temporarily (15). Thus, interest in identifying

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other strategies for BCC chemoprevention in high-risk populations remains high.

Topical retinoid therapy is a potentially attractive alternative to oral retinoids. Tazarotene (Tazorac, Allergan) is a retinoid with relative specificity for RAR-β and RAR-γ receptors. In one open label trial of the efficacy of topical tazarotene versus BCCs, 10 of 19 tumors improved histologically, and 3 tumors were cured after 3 months of treatment with tazarotene (16). In a separate study, Tazorac caused complete histologic and clinical resolution in 16 of 30 BCCs when applied for as long as 8 months (17, 18). Topical tazarotene reduced the number and size of murine microscopic BCCs by 85%, and the treated mice developed essentially no visible BCCs (19). Eight of 10 untreated macroscopic BCC tumors obtained from Ptch1$^{+/-}$ mice expressed RAR-γ, suggesting that tazarotene-RAR-γ–induced transcriptional changes may underlie the observed efficacy (20). Our data suggest that inhibition of phosphoinositide 3-kinase (PI3K)/Akt signaling is an important downstream mechanism for this inhibition (So et al.). Nevertheless, genetically engineered preclinical models may fail to predict the true efficacy of an agent in a human population due, among other things, to cross-species variation in levels of tumor cellular components or differences in tumor stroma (21). Notably, the recent Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial, a randomized controlled study comparing the efficacy of another topical retinoid, tretinoin, versus vehicle control in a high-risk population of 1,311 subjects, failed to demonstrate any significant difference in the primary endpoint of time to new BCC (22). We report here the results of our 2 concurrent human trials designed to evaluate both the chemopreventive and chemotherapeutic efficacy of topical tazarotene in high-risk patients with BCNS.

Materials and Methods

Chemoprevention of BCCs of the chest: study design

We evaluated the efficacy of tazarotene for BCC chemoprevention in a phase II, randomized, double-blind, vehicle-controlled, crossover study conducted at 4 clinical centers (Clinicaltrials.gov identifier: NCT00783965). The Institutional Review Boards at Children's Hospital Oakland Research Institute (CHORI) and at the College of Physicians and Surgeons at Columbia University Medical Center approved both trials. Between June 2006 and January 2010 we screened 42 and enrolled 34 patients with a diagnosis of BCNS. Patients were diagnosed with BCNS based on clinical criteria per Kimonis and colleagues, rather than by PTCH1 sequencing (23). Patients provided informed consent, had their BCC burden evaluated, and were randomized into treatment groups at their initial visit. Patients and investigators were blinded to treatment assignments. The randomization was in a 1:5 ratio to either treatment arm 1, entailing 12 months of tazarotene 0.1% cream applied once daily followed by 24 months of vehicle cream once daily, or treatment arm 2, entailing vehicle cream applied once daily for 12 months followed by 24 months of tazarotene 0.1% cream daily (Fig. 1). We instructed participants to apply the cream only to their chest and specifically to avoid applying it to their backs.

Chemoprevention of BCCs of the chest: primary and secondary endpoints

The primary statistical endpoint for chemoprevention was the proportion of patients in whom fewer BCCs developed on the chest during their 2 years of tazarotene treatment as compared with the preceding 1 year of vehicle treatment. This analysis was performed on patients in treatment arm 2 only; arm 1 patients were utilized primarily to allow for double blinding. To account for nontreatment–related intraindividual variation in the rate of BCC development over time, the change in the chest BCC count was normalized for each individual relative to the change in the back BCC count. Thus, we defined, a drug "responder" as a patient who had a 50% or greater reduction in normalized chest lesion accumulation during tazarotene treatment versus during vehicle treatment.

To determine patient drug responder status, we first calculated the average monthly percentage change in the number of BCCs between the start and end of the *vehicle* application period for each individual on the back and chest separately. The longest diameter of BCCs $\geq$3 mm were identified and include BCCs $\geq$3 mm that were surgically excised or otherwise individually treated during the period of observation either by the patient's primary skin care provider or by study investigators. For calculations, we used the average of 2 successive visits at the start (months 1 and 3) and end (months 9 and 12) of the vehicle application period in order to improve the precision of lesion counts.

Similarly, the monthly percentage changes in the total number of BCCs $\geq$3 mm on the back and chest were calculated for the active tazarotene treatment period for each individual. Again, this represents the 24-month period during which tazarotene was applied to the chest, with the back left untreated.

Using these parameters, a patient was classified as a responder if his or her BCC count satisfied the following relationship:

$$\frac{\Delta P_{\text{back 2}}}{\Delta P_{\text{back 1}}} > 2\frac{\Delta P_{\text{chest 2}}}{\Delta P_{\text{chest 1}}} \qquad \text{(A)}$$

where ΔP_{back1} and ΔP_{chest1} are the average monthly percentage changes in the total number of BCCs $\geq$3 mm during application of vehicle cream. ΔP_{back2} and ΔP_{chest2} are the average monthly percentage changes in the total number of BCCs $\geq$ 3 mm during application of tazarotene cream. Thus, the threshold for tazarotene chemoprevention efficacy was defined *a priori* as a minimum of a 50% response rate in arm 2.

Secondary endpoints included analysis of differences in tumor burden, defined as the total sum of the longest diameters of all lesions present at a specific time point, between vehicle and active treatment.

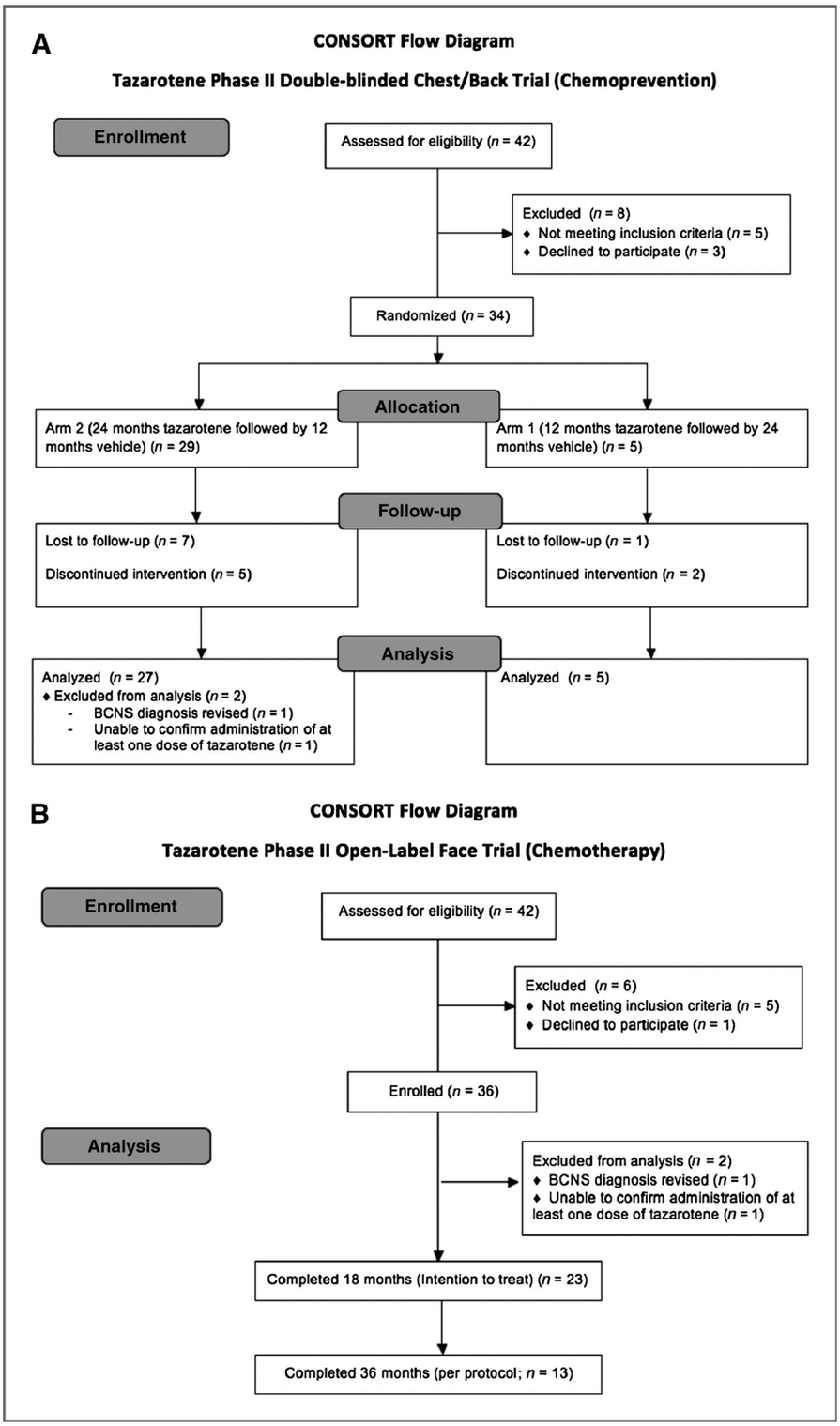

Figure 1. Consort flow diagram of patients with BCNS in the double-blinded chest/back chemoprevention trial (A) and consort flow diagram of patients with BCNS in the open label face chemotherapy trial (B).

Chemotherapy of target lesions and of BCCs of the face: study design

The efficacy of tazarotene for chemotherapy of existing BCC lesions was evaluated using a separate phase II, single arm, open-label study conducted concurrently at the identical study sites (Clinicaltrials.gov identifier: NCT00489086). All 42 individuals with BCNS screened for the chemoprevention trial were concurrently offered

the opportunity to participate in the chemotherapy trial so long as they had a treatable BCC "target" lesion ≥3 mm in longest diameter in a location other than the face, chest, or back. We enrolled 36 patients in this open-label study, which included 33 of the 34 patients involved in the chemoprevention study and 3 additional patients who elected to participate only in the chemotherapy study. Patients were instructed to apply tazarotene 0.1% cream daily to the specified "target" lesion and to the entire face for a total of 18 months. Patients were observed for an additional 18 months (no topical application), during which they continued to return for interval assessments every 3 months.

Chemotherapy of target lesions and of BCCs of the face: endpoints

The primary endpoint used to evaluate tazarotene efficacy for BCC chemotherapy was the complete response rate, defined as the complete visible disappearance of a patient's "target" lesion during the 18 months of tazarotene application and its failure to recur during the ensuing 18 months. We defined surgical removal of a target lesion as a treatment failure. The primary endpoint was assessed based on intention to treat analysis such that any subject who underwent the baseline evaluation and applied at least 1 dose of tazarotene was included in the analysis. Drop outs were considered nonresponders. *A priori* treatment success for tazarotene was defined as a complete response rate of at least 50%, and treatment failure was defined as a complete response rate of 25% or less.

Secondary endpoints included time to lesion clearance, time to lesion progression, duration of complete response, and the overall response of treated lesions. The study also evaluated the incidence of new BCCs on the face as a tertiary chemoprevention endpoint. We quantified the change in BCC count and burden on the face using a logistic regression model with repeated measurements, and comparison was made to the corresponding changes seen on the untreated back.

Clinical assessments

We examined the skin of the chest, back, and face every 3 months throughout the trial. The chest was defined as the skin from the clavicles to the areolae, excluding the skin of the intermammary cleft. The back was defined as the skin from the top of the scapula to T9/T10 (the level of the umbilicus). The face was defined as the skin from the frontal hairline (if balding, no more than 10 cm above the eyebrows) to the jawline and from one ear to the other except for the periorbital area, defined as the area below the eyebrows to 2 cm below the free edge of the lower lid. Each BCC lesion identified was measured at its longest diameter, mapped on a body map diagram, and photographed to ensure clinical consistency at subsequent visits. Because the protocol allowed patients to have BCCs excised by their primary skin care physician based on clinical need, documentation of excised lesions was obtained whenever possible, and a mathematical assumption was made that the patient carried forward the excised lesions into the future at the previously recorded size. Adverse events were recorded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Compliance assessments

To gauge compliance, patients returned their previously used tubes of study medication and received new tubes at each 3-month interval visit. The average amount of medication used was estimated by comparing the weights of used tubes to the known weight of unused tubes of tazarotene. Based on the body surface area of the chest and face, we estimated that it would require 30 and 15 g of topical therapy per month to treat the entirety of the chest and face daily. Compliance was defined as an average monthly usage at least 75% of that expected. We selected the frequency of dosing for our study based on the daily dosing used in previous mouse studies that demonstrated therapeutic efficacy with tazarotene (19).

Statistical analysis

For the chemoprevention trial of the chest, sample size calculation was based on the 2-sided exact Fisher binomial test. We initially assumed a treatment group of 35 subjects in arm 2 for evaluation of the primary endpoint, with an additional 7 patients randomized to arm 1 to allow for blinding. Using a drop-out rate estimated at 33%, we expected 24 subjects in arm 2 to complete the 36-month trial. With a type I error of 0.05 and a 2-sided test, a sample size of 24 subjects would have a statistical power of 84% to test the hypothesis of percentage of responders ≤20% versus percentage of responders ≥50%. The primary endpoint—the proportion of responders—was analyzed using a 2-sided binomial exact test with the null hypothesis of percentage of responders ≤20% and the alternative hypothesis of percentage of responders ≥50%, which was the *a priori* criterion set for clinical efficacy. Differences between rates of BCC development measured in the secondary analysis were analyzed with Student *t* test. No interim analysis was performed for this study.

The sample size for the chemotherapy trial of target lesions and of the face was calculated based on the primary endpoint of complete response rate using a one sided *Z* test with 80% power and 5% type I error rate. Assuming that each subject had one targeted BCC lesion, a minimum of 26 patients would be needed to reject a null hypothesis of ≤25% complete response rate against the alternative ≥ 50% complete response rate. An interim analysis was performed when 10 subjects completed the 36-month trial.

Results

Study patients

From June 2006 to January 2010, we screened 42 candidates. Ultimately, 34 patients with BCNS were enrolled and

Table 1. Characteristics of 34 patients with basal cell nevus syndrome in chemoprevention trial

Characteristic	Tazarotene arm 2 ($N = 29$)	Tazarotene arm 1 ($N = 5$)	*P* value
Age (year)—mean ± SD	51 ± 13	54 ± 7	NS
Male—no. (%)	15 (52)	2 (40)	NS
Last follow-up (month)—mean ± SD	28 ± 11	17 ± 17	0.07
Number of BCCs at baseline—mean ± SD			
Back	12 ± 12	10 ± 9	NS
Chest	6 ± 4	5 ± 2	NS
Face	7 ± 6	13 ± 18	0.15

NOTE: Arm 2, 24 months tazarotene followed by 12 months vehicle; Arm 1, 12 months tazarotene followed by 24 months vehicle.
Abbreviation: NS, not significant.

randomized in the chest chemoprevention trial (Fig. 1A, CONSORT diagram). Participants in the 2 arms of the randomized chemoprevention trial were similar at baseline in age, gender, and number of BCC tumors on the face, chest, and back (Table 1). We analyzed data from 32 of 34 enrolled subjects, excluding one subject as non-BCNS diagnosis and one for dropping out before month 1. The 32 participants had a mean follow-up duration of 26.4 months and 18 (55%) participants completed the full 36-month trial. Reasons for drop-out included logistical difficulties of attending follow-up visits, loss to follow-up, enrollment in another clinical trial, and noncompliance. No patients withdrew from the trial due either to adverse events or to inability to tolerate treatment side effects. Adverse events during this trial were minor (grades 1 and 2 only) and of the type previously reported—skin dryness, irritation, peeling, and erythema (Table 2). We did not observe a correlation between adverse events and a therapeutic response.

For the open label chemotherapy of target and facial BCCs, we excluded data from the same 2 patients, thus including 34 of the 36 individuals in the intention-to-treat analysis (Fig. 1B, CONSORT diagram). This group had a mean follow-up of 23.6 months; 19 (56%) completed the full 36 month trial. Because most subjects participated in both trials concurrently, reasons for drop out closely resembled those occurring in the chemoprevention trial. Thirty-three individuals were enrolled concurrently in both trials, whereas 3 patients chose to participate solely in the chemotherapy trial.

Clinical response in the chemoprevention trial of the back and chest

Twenty-seven of 32 eligible patients randomized to treatment arm 2, the arm prespecified for efficacy analysis, were assigned to receive 12 months of vehicle cream treatment followed by 24 months of tazarotene cream treatment to the chest. At baseline, this group had a mean (± SD) of 6 ± 4 tumors on the chest and 12 ± 12 tumors on the back (Table 1).

Sixteen of the 27 eligible patients in arm 2 completed the full 36 months of follow-up and thus were accessible for analysis of the primary endpoint comparing the effect of 2 years of tazarotene treatment against the 1 year prior of vehicle treatment (Fig. 2). Based on this analysis, only 1 patient (6.3%) qualified as a responder. Using the BCC counts measured at the beginning and end of the active treatment periods, we calculated the monthly percentage increase in total number of BCC tumors on the chest during tazarotene treatment to be 2.2% ± 1.0% for those patients who completed the study ($N = 16$). This result was not statistically significant compared with the monthly percentage change observed during the control vehicle treatment period, −0.7% ± 2.1%. The single responder experienced a reduction in the monthly percentage change in BCC count on the chest from 11% during the vehicle period to −2% during the active treatment period, with a constant rate of change in BCC count on the back over the 3 years. To qualify as a responder according to Equation (A), a subject needed to have a monthly percentage change in BCC counts on the chest during tazarotene versus vehicle treatment that was *50% or less* of the similar ratio of the changes on the

Table 2. Grades 1 and 2 adverse events, No. (%)

Adverse event	Tazarotene arm 1 ($N = 5$)	Tazarotene arm 2 ($N = 29$)	*P* value
Edema	0 (0)	1 (4)	NS
Erythema	2 (40)	4 (14)	<0.001
Dryness	0 (0)	6 (21)	<0.001
Inflammation	1 (20)	0 (0)	NS
Itching	0 (0)	3 (10)	<0.001
Irritation	2 (40)	4 (14)	<0.001
Peeling	0 (0)	4 (14)	<0.001
Rash	0 (0)	4 (14)	<0.001

NOTE: Arm 2: 24 months tazarotene followed by 12 months vehicle; Arm 1: 12 months tazarotene followed by 24 months vehicle.
Abbreviation: NS, not significant.

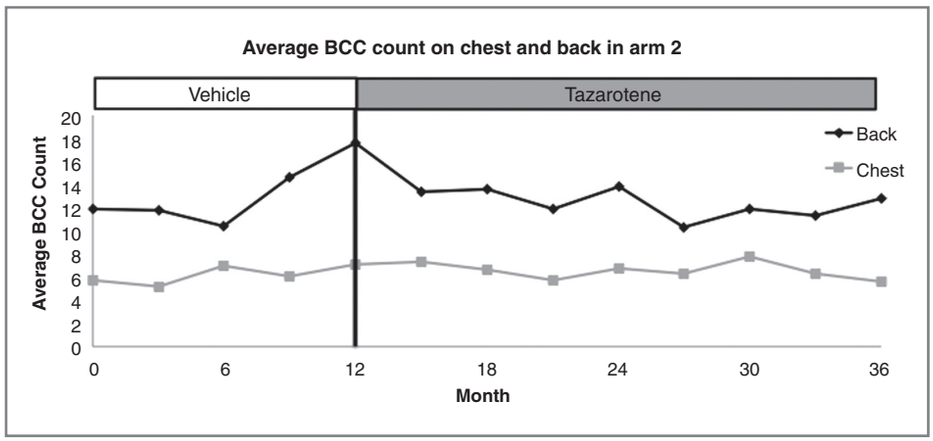

Figure 2. Average lesion counts over time on chest and back. All 28 patients in treatment arm 2 included in this analysis, including 12 patients who did not ultimately complete the entire trial. The vertical line represents the timepoint when patients began active treatment with tazarotene cream on the chest only. Back received no treatment during the entire 36 months.

untreated back. In exploratory analyses, we relaxed this threshold to between 10% and 50% and still saw no change in the number of patients qualifying as a responder, suggesting that the low responder rate was not simply a result of a stringent definition. Two of 5 patients completed the full 36 months of follow-up of arm 1, where patients received 12 months of active tazarotene followed by 24 months of vehicle. Both patients experienced reduction in BCC counts on the chest and a constant rate of change in BCC counts on the back over the course of active treatment.

Secondary analysis was performed to assess tazarotene's effect on the BCC tumor *burden*, which we defined as the sum of the longest diameters of all lesions ≥ 3 mm. We used the previous definition of a responder (Eq. 1), this time replacing BCC count with burden, and observed an identical result in that 1 of 16 patients (6.3%) qualified as a responder. This individual was the same patient who qualified as a responder using BCC counts in the original responder analysis. As a group, the 16 patients who completed the trial experienced an increased monthly percentage change in *burden* of $3.0\% \pm 1.4\%$ on the chest during the active tazarotene treatment, which was not statistically different than the $1.3\% \pm 2.9\%$ per month experienced during the vehicle treatment period.

In exploratory analyses using all 27 eligible subjects in arm 2, including those who withdrew from the study early, we calculated a monthly percentage change in BCC count by taking the percentage difference between the initial and terminal time points of each treatment period. We used linear regression to determine the monthly change in BCC counts for each patient on both the chest and back. We found that the rate of BCC development per month did not differ between the chest (with or without tazarotene) relative to the back. Furthermore, we observed no late-peaking reduction in the rate of BCC development on the chest during the 2 years of active tazarotene treatment.

Clinical response in the chemotherapy trial of target lesions and of the face

Thirty-four patients were included in the intention-to-treat analysis of the primary endpoint, which evaluated tazarotene's efficacy in visible resolution of target BCC lesions (Fig. 1B, CONSORT diagram for open label trial). The mean ($\pm$ SD) initial target lesion diameter was 6 ± 7 mm. Twenty-three subjects completed 18 months of the trial (68%). Ultimately, only 2 of 34 patients achieved complete resolution of their target lesion (complete response rate = 5.9%). Although most patients in the chemotherapy trial were the same patients in the chemoprevention trial, the 2 responders described here are different than the single responder from arm 1 of the chemoprevention trial. Based on the trial's *a priori* criterion for efficacy, tazarotene was ineffective as chemotherapy for BCCs. The 2 responders' lesions were both initially 3 mm in diameter, with resolution occurring at months 3 and 12, respectively. Two additional patients experienced resolution of their target lesion but did not qualify as a complete response because resolution occurred during the subsequent observation period rather than during the 18 months of active tazarotene application. These patients' lesions resolved 9 and 15 months after their last application of tazarotene, respectively, and thus resolution could not be attributed with confidence to the effect of the study medication. We did not observe recurrence of the 4 resolved target lesions.

Only 13 subjects completed the entire 36-month trial (first 18 months tazarotene, months 19–36 observation). This group had a complete response rate of 15%, which still does not meet the *a priori* criterion for efficacy. We did not collect biopsies to assess for biomarker response.

Treatment compliance

We weighed returned tubes of cream from 12 randomly selected subjects. Using the compliance criteria stated above in the Materials and Methods, we found that 4 of 12 patients (33%) qualified as being compliant. The average ($\pm$ SD) amount of cream used per month was 26.7 ± 10.3 g (among this group range 11–49 g) on the chest, which is approximately 40% lower than the amount we would have expected with optimal medication usage at once daily dosing.

Discussion

Despite our past findings of robust anti-BCC effects of topical tazarotene in Ptch1$^{+/-}$ mice and others' identification

of significant anti-sporadic BCC effects in humans, our data indicate that topical tazarotene did not have clinically significant anti-BCC effects in PTCH1$^{+/-}$ humans. In both the chemoprevention and chemotherapy trials, tazarotene clearly failed to meet our *a priori* defined criteria for treatment success.

The reasons for this disparity between our human and mouse data are uncertain but they are consistent with our recent findings of strong anti-BCC effects of topical Cu-61414 in our Ptch1$^{+/-}$ mice with a topical preparation that was ineffective in treating human sporadic BCCs (24). One of the potential contributors to disparity in that Study is a differential effect of the drug on mouse versus human target protein, an explanation that potentially could account in part for the disparity in this study as well. Other possibilities include the superior barrier function of human stratum corneum, the greater thickness of human dermis, and the potentially lesser compliance of human subjects. Tazarotene's known efficacy against acne and psoriasis and its causing cutaneous inflammation in humans indicates that there is some percutaneous absorption. However, it is unknown whether the dermal drug concentration required to obtain those effects is similar to that needed for anti-BCC efficacy. It is clear that the patients used the drug to tolerance. Furthermore, because of their high likelihood of developing more BCCs, the patients in these trials were likely to be highly motivated to use as much of the agent as possible.

Limitations of the study include the high dropout rate, low compliance of topical application, and the uncertain applicability of our results to sporadic BCCs. Our results differ from previous studies in that most of our target BCCs were nodular, whereas 65% of BCCs in the study by Chimenti colleagues were of the superficial subtype. Also, that study used tazarotene gel rather than cream, which could have improved drug penetration. Another limitation was the lack of biomarker studies or dose-ranging studies in fewer subjects to identify the optimal dosage and excipients for maximal anti-BCC response. Furthermore, we cannot exclude differences in response to tazarotene between sporadic versus BCNS BCCs (25–28).

Only 16 patients completed the trial, thus reducing the power of our study from 80% to 61%. Our results do not invalidate the underlying hypothesis that topical retinoids can have a significant anti-BCC effect, but do suggest that they are not likely to be a practical approach in humans. Perhaps selecting targets downstream of those modulated by retinoids might diminish the dose-limiting irritation associated with topical retinoids. Our accompanying paper (So and colleagues) identifies the PI3K/AKT/mTOR signaling pathway as a downstream target pathway of tazarotene's action and the efficacy of PI3K inhibitors against murine BCCs but the relevance of murine models, no matter how closely they seems to mimic human disease, is uncertain (29,30). We believe that murine models can provide mechanistic insights and can serve as screens for therapeutic approaches but clearly cannot substitute for studying drug effects *in vivo* in humans. Future clinical trials should focus on preliminary studies to ensure dose-dependent topical drug uptake on human skin in addition to positive murine results.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.Y. Tang, M. Aszterbaum, D.R. Bickers, E.H. Epstein
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.Y. Tang, A.S. Chiou, A.M. Chanana, W. Lee, B.J. Thompson, D.R. Bickers, E.H. Epstein
Writing, review, and/or revision of the manuscript: J.Y. Tang, A.S. Chiou, J.M. Mackay-Wiggan, A.M. Chanana, J.A. Lindgren, B.J. Thompson, E.H. Epstein
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