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Efficacy of posaconazole for treatment of nodular basal cell carcinoma

AM. Kabsha[1]*, AG. Eguiluz-Meléndez[2], F. Gushken[3], G. Rosa[4], H. Elazaly[5], LF. de Oliveira[6], MC. Zanon Zotin[7], MA. Vásquez[8], LRG. Ferreira[9], AG. Tarantino[10]

**Corresponding author: Ahmed M Kabsha, [Ebn Sina Medical] email: elhossiny@hotmail.com*

Rest of author's affiliation at the end of the manuscript.

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Abstract:

Background: *Basal cell carcinoma (BCC) is the most commonly diagnosed skin cancer, with increasing incidence each year. Although the treatment of BCC is typically surgical, a non-surgical approach is highly desirable for patients with non-aggressive BCC recurrence, multiple tumors, poor general health, or with lesions in vulnerable areas. In the last few years, advanced cancer treatment options have targeted the Hedgehog pathway, known to regulate the proliferation of cancer stem cells and increase tumor invasiveness. Itraconazole, a triazole antifungal that inhibits ergosterol synthesis in fungi, have also proven a clinically significant tumor size reduction in BCC via inhibition of this pathway. However, serious adverse effects might preclude itraconazole use in broader population where multiple medications or comorbidities might be present. Preliminary studies demonstrate posaconazole, another member of the triazole family, may present a safer clinical alternative to the currently used pharmacological methods utilised in the management of BCC. Therefore, this phase II study aims to analyze the efficacy of posaconazole as a safe therapeutic option for nodular BCC lesions.*

Methods: *This is a study protocol designed as a single center, randomized, double-blinded, placebo-controlled trial. Patients over 18 years of age, diagnosed with at least 2 nodular BCC lesions and that are awaiting to undergo surgery are eligible to participate in this phase II study. Before undergoing surgical excision, 170 patients (1:1 allocation) will be randomized to receive 800 mg daily of posaconazole or placebo for four weeks.*

Discussion: *The main strengths of this study are the potential to increase general understanding of the therapeutic and metabolic impact of posaconazole. The results from this trial may also provide valuable insights to guide a larger clinical trial of posaconazole for inoperable BCC. The main limitations of the study consist of the limited intervention time frame of four weeks and the sample representativeness since it is a single-center study of patients with nodular BCC.*

Keywords*: Basal cell carcinoma, posaconazole, hedgehog pathway, p53, Ki67*

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INTRODUCTION

Basal cell carcinoma (BCC) is the type of skin cancer most commonly diagnosed with an estimated incidence of 4.3 million cases in the United States (US) each year (Kim et al., 2014; Rogers, Weinstock, Feldman, & Coldiron, 2015; American Cancer Society, 2016). The estimated cost of skin disease in the US alone is approximately $8.1 billion annually; non-melanoma skin cancers comprise over half of this cost at $4.8 billion per year (Guy, Machlin, Ekwueme, & Yabroff, 2015). Untreated BCC is a risk factor for melanoma, a potentially deadly disease (Puig & Berrocal, 2015).

Although the treatment of BCC is typically surgical, a non-surgical approach is highly desirable in cases of non-aggressive BCC recurrence, patients with multiple tumors (Gorlin Syndrome or other syndromes with multiple BCCs), patients with physical conditions precluding surgical procedures, and those lesions occurring in areas where surgery might lead to loss of local function or cosmesis. Among the subtypes of BCC, nodular basal cell carcinoma comprises about 60-80% of the cases and occurs most often on the skin of the head. It also is a less

aggressive histology subtype, which allows for non-invasive treatment before surgical resection.

Many endeavors to study non-surgical approaches to BCC treatment are in progress. Existing research confirms most BCC types have upregulation in the Hedgehog (Hh) signaling pathway. This important metabolic pathway is known to regulate the proliferation of cancer stem cells and increase tumor invasiveness. In the last few years, advanced treatment options for BCC have targeted the Hh pathway (Gupta, Takebe, & LoRusso, 2010).

Vismodegib, sonidegib (smoothened [SMO] inhibitors) and itraconazole (azole antifungal) have been studied as Hh pathway inhibitors. Vismodegib is the first SMO inhibitor, acting on the Hh pathway, to gain approval by the US Food and Drug Administration (FDA), as a therapeutic option for the treatment of metastatic BCC (mBCC) and locally advanced BCC (laBCC) (Puig & Berrocal, 2015).

Itraconazole (azole antifungal), another Hh pathway inhibitor, is currently being explored for its effectiveness in the treatment of BCC. Triazoles inhibit antifungal growth by its potent antagonism of 14-α-lanosterol demethylase (14LDM), an enzyme required for ergosterol biosynthesis in fungi (Tatsumi et al., 2013; Chen et al., 2016). It has been reported that itraconazole (and posaconazole) inhibits the Hh pathway by a mechanism distinct from its antifungal activity, through inhibition of Hh reception between PTCH (Patched) and SMO in cells depleted of cellular sterols (Lepesheva & Waterman, 2007; Cooper et al., 2003). However, the use of itraconazole is a concern because its primary metabolite, hydroxyitraconazole, acts as both a potent inhibitor of CYP3A4, and weaker inhibitor of CYP2C9 and CYP2C19 (Niwa et al., 2005). This effect may account for dangerous potential drug-drug interactions in elderly patients with multiple drug schemes, and those diagnosed with hepatic and kidney insufficiency (Isoherranen, Kunze, Allen, Nelson, & Thummel, 2004; Templeton et al., 2008). Although Itraconazole has also shown efficacy in inhibiting the Hh pathway, patients with a high risk of heart failure and those with impaired hepatic function are at higher risk of severe adverse effects (Neofytos, Avdic, & Magiorakos, 2010).

Consequently, posaconazole (triazole antifungal) may present a safer alternative to itraconazole and adjunct treatment of vismodegib in the management of BCC (Döring et al., 2014). It has shown synergistic activity with other SMO inhibitors in reducing Hh activity in BCC, thus suggesting a distinct binding region than vismodegib and sonidegib, as well as activity against drug resistant SMO mutants (Chen et al., 2016). Posaconazole inhibits CYP3A4, but does not inhibit other CYP enzymes (CYP 1A2, 2C8, 2C9, 2D6, or 2E1), and has shown to be well tolerated orally in phase I trials (Wexler et al., 2004). Posaconazole is expected to have fewer drug-drug interactions and no dose adjustment requirements for mild-moderate kidney/hepatic insufficiencies (Katragkou, Tsikopoulou, Roilides, & Zaoutis, 2012; Raad et al., 2006). In addition, patients undergoing posaconazole treatments for up to two years with no significant adverse events have been reported, an important consideration as continuous, prolonged regimens of therapy will most likely be needed for cancer treatment (Anstead, Corcoran, Lewis, Berg, & Graybill, 2005). However, to date, no clinical study for BCC treatment with this drug has been performed.

Therefore, the primary objective of this trial is to assess the efficacy of oral posaconazole (800 mg daily) against placebo on the change of thickness of nodular BCC lesions in newly diagnosed patients. Secondary objectives consist in the assessment of posaconazole safety and measurement of the effect of posaconazole on the proteins p53 and Ki-67 (proliferative marker as inhibitor biomarkers of the Hh pathway).

METHODS

Study Design

This phase II clinical trial proposed study protocol of a currently unplanned study is designed as a single center, randomized, double-blinded, placebo-controlled trial comparing posaconazole and placebo on the change of BCC tumour thickness at baseline and after 4 weeks as the primary outcome. According to the National Comprehensive Cancer Network (NCCN) guidelines, we will assess patients with low-risk of recurrence BCC, who meet this study's eligibility criteria and are awaiting surgery. The four-week trial time frame was chosen because it does not interfere with current standard treatment guidelines for this type of skin cancer and given the non-urgent nature of this condition, patients will typically experience the same amount of waiting time before being scheduled for a surgical procedure of this nature. Furthermore, Kim et al. (2014) demonstrated a four-week intervention with itraconazole signalled reduction and non-progression of tumour size within this period. We hypothesise the same will be possible with posaconazole, minus the additional side effects of itraconazole especially in older patients and those with concomitant drug schedules. Participants will be randomized in a 1:1 manner to either 800 mg of oral posaconazole daily or oral placebo pills for four weeks

before undergoing lesion surgical excision (Miller et al., 2010).

Intervention

The studied intervention is the delivery of oral posaconazole (800 mg daily, given orally, 400 mg BID), to increase the bioavailability and serum concentration of the drug (Ezzet et al., 2005) (intervention group) or a placebo pill (placebo group) with similar appearance for four weeks. The 800 mg dose was the highest demonstrated safe dose in previous clinical trials (Jancel, Cao, & Diak, 2016) and given the short time of this intervention, the authors deem appropriate to attempt detection of tumour thickness change post intervention.
Figure 1 (appendix) explains the study procedure. After undergoing eligibility screening and informed consent, patients will be randomized into intervention or control group. Week 1 includes a patient visit and examinations will be conducted to evaluate baseline measures (tumor thickness, p53 and Ki-67, BG, LVT, GFR and ECG). Week 2 consists of a safety-screening visit, including BG, LVT, GFR and ECG monitoring. Week 3 includes a phone follow up to check for safety. Finally, week four includes the final patient visit and data collection (BG, LVT, GFR and ECG).

Endpoints

The primary outcome is the measurement of tumor thickness reduction or delta of the non-biopsied nodular lesion, measured at baseline and after four weeks of treatment using a high-frequency ultrasound probe (HFUS) (20 MHz). The use of the HFUS to define the BCC thickness has been validated (Pelosini et al., 2015). The correlation between the BCC thicknesses measured by HFUS and histologically reported are 90-98% (Bobadilla et al., 2008; Crisan et al., 2013). To avoid the interrater variability in this single center study, one rater will be appointed to do the HFUS tumor thickness measurement procedure.

The secondary outcomes are immunohistochemistry assessment of p53, and Ki-67 biomarkers (measured at baseline and upon intervention completion), performed in the biopsied tissue at baseline and after surgical removal. The difference in the proportion of positivity between the two samples from each patient will be evaluated. Both p53 and Ki-67 are directly related to tumour development and growth and are thus clinically significant biomarkers.

Similarly, a safety profile of oral posaconazole will be assessed after four weeks evaluating QT interval measured with an EKG, liver enzyme levels, kidney function measured by GFR, and blood glucose levels.

Eligibility Criteria

Patients must be over 18 years of age, diagnosed with at least two BCC nodular lesions (according to the NCCN clinical practice guidelines on cutaneous basal cell and squamous cell carcinoma criteria), awaiting surgical intervention (Miller et al., 2010). Patients must be able to fully understand all of the necessary trial information and sign the informed consent form.
Patients will be excluded from this study for any of the enumerated criteria:

1. Undergoing chemotherapy, radiotherapy or immunotherapy for other malignancies;
2. Immunosuppression (due to illness or medication);
3. Allergies to any study components;
4. Undergoing any other treatment with any medication that has a contraindication, potential drug-drug interactions, or increases the QT interval;

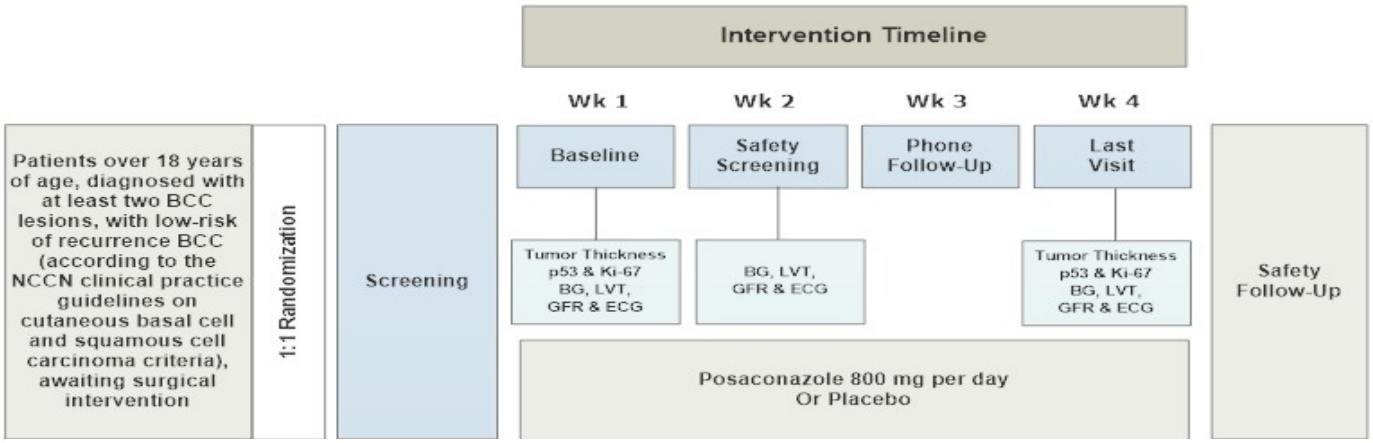

Fig. 1 BG: Blood glucose; LVT: Liver function test; GFR: Glomerular filtration rate; ECG: Electrocardiography

5. Participation in any other trials in the last 30 days;
6. Potential pro-arrhythmic pathologies;
7. Liver disease (history of any acute or chronic liver disease and/or elevated liver enzymes at baseline exams) and/or moderate or severe renal impairment (GFR less than 60mL/min/1.73m2) (Merck, 2019);
8. Pregnancy or breastfeeding. Women of childbearing age must be using at least two contraceptive methods throughout the trial period because posaconazole has shown a teratogenic effect in animal studies and its pharmacokinetics in pregnancy are not yet well understood (Pilmis et al., 2015);
9. Any form of substance abuse, psychiatric disorder, or other condition that may invalidate communication with designated study personnel, including use of benzodiazepines.

Recruitment Strategy

The recruitment process will occur over a six month period, leveraging four main recruitment strategies:

1. Skin cancer clinics and clinician invitation letters;
2. Online advertisement campaign, via Facebook and Google Adwords leading to a website where patients are able to self-report for eligibility triage against the inclusion and exclusion criteria for this trial (Edwards, 2010);
3. Trial registration at both the NHMRC https://www.australianclinicaltrials.gov.au and the NIH https://clinicaltrials.gov websites;
4. Relevant area community announcements through leaflets and posters.

Adherence

At the onset of the medication prescription, patients will receive training with compliance officers. A medication electronic monitoring system (MEMS) pillbox will be given to each participant, along with an A5 poster fridge magnet with skin cancer prevention strategies and an emergency telephone number for reporting of any adverse reaction(s) (Shiovitz et al., 2016). To ensure proper adherence and avoid attrition, patients will be advised to set up alarms to remind of the pills and to keep an updated journal. Patients will also be given the option to receive an automatic text message and/or email reminder (b.i.d.) requesting their reply when they have taken the treatment in order to optimise compliance. Patients will be notified via telephone call, voice and text messages about their clinical visits at baseline, week two and week four.

Randomization

This trial will utilise stratified block randomization, considering lesion thickness as a stratum, stratified block randomization, considering lesion thickness as a stratum with 2 strata less than 2mm tumor thickness and 2mm or more according to Breslow (Breslow, 1970) thickness as recommended by the Stanford criteria (Stanford Health Care, 2019) of high-risk tumor using a third party, online, randomization service (www.sealedenvelope.com).

Blinding

Patients, as well as the whole study team, except safety officers, data safety monitoring board (DSMB) and dispensing pharmacists, will be blinded to the treatment allocation received. A coordinator will be nominated to check data during the whole study. Blinding assessment will not be conducted due to limited amount of data, as well as score and scale weakness of blinding tests.

Emergency Unblinding

Emergency unblinding will occur for safety reasons in a protocoled process in cases of life-threatening or severe side effects. Unblinding can be made upon request by the investigator or any emergency room doctor assisting the patient, using a 24/7 helpline. Where possible, the patient allocation will be revealed only to an assisting doctor not involved in the study. The patient will be automatically excluded from the trial, and their data will be analyzed as per intention to treat analysis. As per the unblinding protocol, the investigator will report the case using an online form made specifically for this purpose.

Sample Size Calculation

Based on Hinz et al. (2012) pilot findings, we estimate that the BCC lesion thickness in the placebo group is 1.03 mm (SD= 0.51) at baseline and after 4 weeks; in the posaconazole group, the BCC lesion thickness is 1.03 mm (SD= 0.51) and 0.7828 mm (SD= 0.51) at baseline and after 4 weeks consecutively, measured by a 20 MHz high-frequency ultrasound HFUS before treatment. An effect size of 24% reduction of the BCC lesion thickness is estimated based on an open-label, exploratory phase II trial (Kim et al., 2014), which showed a 24% reduction in the BCC lesion thickness in the itraconazole group compared to the placebo group. Using a two-sided power analysis for two sample means t-test for the two groups BCC lesion thickness delta (StataCorp. 2017, Stata Statistical Software: Release 15. College Station), we calculated that a sample of 68 patients per group would provide the trial with 80% statistical power to maintain a type I error rate of 0.05. Thus, considering a 20% drop out

rate, 85 subjects will be recruited per arm, 170 subjects in total.

Statistical Analysis Plan

The primary outcome is tumor reduction (delta), measured as the difference between the baseline and four week tumor thickness measured by HFUS between the placebo and posaconazole groups. The analysis will be conducted using a two-sided unpaired t-test considering statistical significance with a p-value <0.05. Descriptive statistics will be reported, and parametric tests will be used for continuous data based on the central limit theorem.

For our secondary outcomes, chi-square test we will be used to compare baseline Ki67 and p53 immunopositivity reduction between placebo and posaconazole groups. An unpaired two-sided t-test will be used to compare QT interval measured in an EKG, liver enzyme levels, kidney function measured by GFR, and blood glucose levels analyzed at week two and four between the two groups, with a required statistical significance with a p-value <0.05.

The most common side effects for short-term use of posaconazole (oral suspension) are mild and include nausea, vomiting, abdominal pain, elevated liver enzymes, headache and abdominal pain. Patients will be instructed to self-report any adverse reactions at any time and will be able to reach out to a 24/7 helpline. More details are included in the eemergency unblinding and dDSMB (Clark, Grim, & Lynch, 2015). Adverse effects will be further categorized with the Common Terminology Criteria for Adverse Events (CTCAE) scale. The comparisons between groups will be performed with a chi-square test.

Since previous reports have evaluated the efficacy of itraconazole (Kim et al., 2014) and vismodegib (Sekulic et al., 2012) after 1-2.4 and 10 months of treatment, respectively, we believe that either an efficacy or a futility interim analysis after 2 weeks may underestimate the posaconazole treatment effect. Therefore, will not perform an efficacy or futility interim analysis. Instead, an interim analysis for safety will be done after two weeks of treatment, and in case serious adverse effects are present in the posaconazole group, the DMSB may decide to interrupt the trial in agreement with the trial sponsor and principal investigator.

Data management

Trial data will be collected, pseudonymized and documented soon after measurement by the investigator in the electronic case report form (eCRF). Entering data may be delegated to members of the trial team. The principal investigator will systematically check against written standard operating procedures (SOPs), all incoming trial data for consistency, omissions, and protocol compliance.

Source data is defined as all the information in the original records, as well as any certified copies. All data must be available at the trial centre to authenticate the existence of the study participants and substantiate the integrity of all data in the trial database. The electronic trial database will be archived for ten years but will remain the property of the study sponsor at all times.

The trial is of short duration with low dropouts expectancy and the sample size was calculated with a 20% margin (to account for possible patient dropout). Therefore, missing data will be treated as complete case analysis, in which all data will be analyzed.

Trial Monitoring

The trial site will be monitored through regular visits by the local coordinating centre for clinical studies to ensure data collection quality, protocol adherence, and appropriate documentation and reporting compliance meet good clinical practice (GCP) standards.

Data Safety Monitoring Board (DSMB)

A DSMB of independent experts will be periodically convened to monitor the safety of the trial as well as to provide impartial advice as may be required. Recommendations of the DSMB (even up to the premature termination of the trial due to safety concerns) will be discussed between the principal investigator and trial sponsor.

Legal Requirements of the Study

The study protocol will be submitted to the local Institutional Review Board (IRB) and the Ethics Committee for approval as per applicable SOPs.

Registration

The trial will be registered with *www.clinicaltrials.gov and www.australianclinicaltrials.gov.au*.

DISCUSSION

BCC is a high prevalence disease with a well-established surgical treatment, however surgical excision is not always the best treatment option for all cases. Patients with non-aggressive recurrent lesions, multiple lesions, not suitable for surgical resection due to poor physical status, risk of loss of function, or poor cosmetic results have few clinical management options available. Identifying a safe clinical option for such patients may

have a significant impact on public health and quality of life, thus reducing the medical and economic burden of this disease. This study proposes a novel, ethical and feasible design for a drug with known pharmacodynamics and pharmacokinetics and with evidence of effect in the crucial tumoral signaling (Hh) pathway. The current proposal addresses the need for alternative clinical treatment for this high prevalence disease, which has limited management options.

BCC tumour thickness has been used as a predictor of tumor invasiveness (Niwa et al., 2005) as well as a treatment efficacy (Hinz et al., 2012; Kim et al., 2014). Therefore, the primary outcome (tumor thickness shrinkage) may enhance clinical management of BCC, whilst the secondary outcome (assessment of p53 and Ki-67 biomarkers) may increase the understanding of the metabolic impact of posaconazole in the treatment of these tumors.

One possible limitation of the study is the timeframe of four weeks set for the intervention. It could limit the assessment of the effect size and efficacy. Another limitation is the sample representativeness of the study population. Since this is a single-center study of patients with nodular BCC, this population may not reflect all patients diagnosed with BCC lesions, worldwide.

On the other hand, if the preliminary efficacy and safety of posaconazole is proven in this first ever, proof-of-concept trial, a new therapeutic option for patients with BCC may become a viable alternative. This new approach is especially beneficial for those patients with multiple and/or recurring tumours as treatment with posaconazole in these instances, unlike topical chemotherapy or surgery, may be preventative as well as therapeutic, with lesser side effects compared to the other drug therapy options previously discussed. Furthermore, a positive outcome for this trial helps to inform specific effect size, which can then be further used to calculate an adequately powered, future phase III, comparative, randomized clinical trial for patients with inoperable BCC.

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Author Affiliations

1. Hoffmann-La Roche Ltd, elhossiny@hotmail.com

2 Department of Neurosurgery, Instituto Nacional de Neurología y Neurocirugía "Dr. Manuel Velasco Suárez", Mexico City, Mexico - eguiluz.aldo@gmail.com

3 Faculdade Israelita de Ciências da Saúde, São Paulo, Brazil - gushken@alumni.usc.edu

4 The Rosa Institute, Sydney, Australia, gabriela@naturalfertilitybreakthrough.com

5 Charité University, Berlin, Germany- hisham.elezaly@charite.de

6 Department of Clinical Surgery, Universidade Federal do Amazonas, Manaus, Brazil - eufreireoliveira@gmail.com

7 Ribeirão Preto School of Medicine, University of São Paulo, São Paulo, Brazil - mczzotin@hcrp.usp.br

8 Pontificia Universidad Católica Madre y Maestra, Santiago, República Dominicana - moisesvasquez@outlook.com

9 Universidade de São Paulo, São Paulo - SP, Brazil - lucasrgferreira@gmail.com

10 MANIMA Social Assistance and Healthcare Organization, Milan, Italy - andreagtarantino@gmail.com

Conflict of Interest

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with the submission of the manuscript, the final version has been approved by all authors. The authors have no financial or personal conflicts of interest related to this research subject.

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