A Phase III, Double-Blind, Placebo-Controlled Clinical Trial to Assess Celecoxib as a Chemopreventive Agent Inhibiting Recurrence of Non-Melanoma Skin Cancer

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A. Study Purpose And Rationale

Non-melanoma skin cancer (NMSC), consisting of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most commonly occurring cancer in humans. A major environmental risk factor for the development of NMSC is exposure to ultraviolet (UV) radiation. The incidence of NMSC has been increasing markedly in recent years, likely due to population-wide increases in exposure to UV radiation. For this reason, a safe and effective means of chemoprevention for these tumors would be of considerable benefit.

Cyclooxygenase is the rate-limiting enzyme in the production of prostaglandin from arachadonic acid. Cyclooxygenase exists in two isoforms. COX-1 is a housekeeping enzyme, which is constitutively expressed in most human tissues. COX-2 is an inducible isoform which is believed to play a role in various inflammatory and neoplastic processes (1). Recently, the role of COX-2 in carcinogenesis has become an area of active investigation. COX-2 has been shown to be upregulated in numerous cancers, including colorectal, gastric, breast, prostate, lung, and melanoma. Non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit both COX-1 and COX-2 activity, have been shown in epidemiological studies to decrease incidence of colon, breast, and lung cancer (2,3,4,5). Furthermore, specific inhibition of COX-2 has been shown to play a critical role in the chemoprevention of colon cancer in a murine model for familial adenomatous polyposis (FAP), and the COX-2 specific inhibitor celecoxib has been FDA approved for the clinical treatment of patients with FAP (6).

Current research indicates that COX-2 may also play a critical role in the progression of NMSC. COX-2 is upregulated by acute UVB exposure in human skin, and is increased in human actinic keratoses, squamous cell carcinomas (SCCs), and basal cell carcinomas (BCCs) (7,8). In the murine model, COX-2 expression increases in murine skin in response to chronic UVB exposure, and is increased in benign papillomas, SCCs and BCCs (7,9). Topical administration of a COX-2 inhibitor has been shown to be effective in the attenuation of UVB-induced cutaneous inflammation (10). Oral administration of inhibitors of COX-2 reduces the development of UV-induced murine skin tumors in a dose-dependent manner by up to 89% (11). Significantly, inhibition of new UVB-induced tumors is seen even when celecoxib administration begins following the last dose of UVB, when 90% of mice have at least one tumor. This demonstrates that celecoxib is likely to act at a post-initiation stage of tumor promotion, and may be an effective chemopreventive agent even after significant cutaneous sun damage is present (12).

Patients who present with a history of at least one NMSC are at considerable risk of developing additional NMSCs. Prior studies have indicated that the estimated five-year risk of developing NMSC in patients presenting with at least one prior NMSC is 50% (13,14,15). The most significant risk factor is number of prior NMSCs; the five-year risk ranges from 27% in patients presenting with a first NMSC to 90% in patients presenting with greater than ten prior NMSCs (13). The five-year risk for NMSC in those presenting with BCC is 41%, and in those presenting with SCC is 31%; subsequent NMSCs tend to be of the same histologic type as the presenting NMSC. In addition, the rate of occurrence of NMSC is greatest in the first three years after the initial NMSC and decreases over time (15).

Patients presenting with at least one prior NMSC are therefore an ideal target population for chemoprevention to inhibit formation of subsequent NMSCs. The purpose of this study is to investigate the efficacy of celecoxib as a chemopreventive agent for the secondary prevention of UV-induced non-melanoma skin cancer.

B. Study Design And Statistical Analysis

This study will be a five year randomized, double-blind, placebo-controlled clinical trial investigating celecoxib as a chemopreventive agent for the development of subsequent NMSC in patients with at least one prior occurrence of NMSC. The study sample will consist of consecutive patients diagnosed with NMSC. At the time of diagnosis, patients will be invited to participate in this clinical trial. Participation in the trial will begin one week after excision of the presenting NMSC.

Patients will be randomly assigned to the study group or the control group via block randomization based on whether their initial diagnosis is squamous cell or basal cell carcinoma and based on number of prior occurrences of NMSC. Randomization codes will be generated by the Research Pharmacy at Columbia University. All study personnel will be blinded to the study drug administration. Patients assigned to the control group will receive a placebo pill to be taken twice daily for the duration of the study. Patients assigned to the study group will receive a pill which appears identical to the placebo but which contains 200 mg celecoxib, also to be taken twice daily for the duration of the study. Compliance will be assessed every 3 months using patient surveys, pill counts, and blood tests.

The study population will consist of 448 patients in each group. This sample size allows detection of a 10% reduction in the recurrence of NMSC, i.e. from a projected 5 year occurrence rate of 50% to 40%. This sample size also allows for up to a 10% dropout rate. Patients will not be crossed over between groups, and patients will remain in the study for the duration of the study period, regardless of development of new NMSC.

The primary endpoint will be occurrence of NMSC during the 5 year study period. An additional endpoint will be mean number of NMSC over the 5 year time period. Finally, time to occurrences of NMSC during the 5 year study period will be assessed. Recurrence of the presenting NMSC will not be considered a new occurrence of NMSC.

A chi-square test with 0.05 alpha level will be used to determine if there are significant differences in the incidence of NMSC over the five year study period. Additionally, the non-parametric Wilcoxon rank sum test will be used to compare mean number of occurrences of NMSC in the two groups during the five year study period. Time to occurrence of NMSC will be compared using Kaplan-Meier survival curves. The Cox proportional hazards regression analysis will be used to adjust for predisposing variables between the two groups.

C. Study Procedure

Initial evaluation and enrollment will be performed in the Columbia University Dermatology attending physicians' offices. Participation in the study will begin 1 week after excision of the presenting NMSC. Thereafter, the patient will receive oral administration of either celecoxib or placebo, and will return for a dermatologic exam every 3 months. At each visit, any adverse effects will be noted, and patients will submit to blood samples and pill counts to assess compliance. All patients will remain in the study protocol for the duration of the study period, regardless of incidence of NMSC. Only significant adverse effects or non-compliance will be grounds for dropout from the study.

D. Study Drugs

A. Celecoxib (SC-58635), 200mg p.o. BID for approximately 5 years, formulated in hard gelatin capsules containing 200 mg celecoxib, each identical in size and color.

B. Placebo, p.o. BID for approximately 5 years, formulated in hard gelatin capsules containing placebo, identical in size and appearance to the 200 mg celecoxib-containing capsules.

E. Medical Device

Not applicable.

F. Study Questionnaires

See Figure 1 and Figure 2.

G. Study Subjects

Patients aged 20-65 years with Fitzpatrick Type I, II, III, or IV skin presenting with a first occurrence of NMSC will be eligible for inclusion in this study at the time of diagnosis. The Fitzpatrick skin typing system (Type I through Type VI) categorizes subjects according to their susceptibility to sunburn. Patients who rarely or never sunburn, such as dark-skinned people, are far less likely to develop UV-induced skin cancers, and will be excluded from the study to avoid confounding by other predisposing factors to the development of NMSC.

Patients must be in good health, likely to remain in the area and able to complete the 5 year study. Patients must be willing to abstain from use of topical medications, including corticosteroids, vitamin A derivatives, and/or alpha-hydroxy acids.

Exclusion criteria:

- Regular use of NSAIDs more than 2 times per week
- Known hypersensitivity to NSAIDS or COX-2 inhibitors
- Active gastrointestinal disease precluding use of a COX-2 inhibitor
- Prior diagnosis of a gastrointestinal ulcer
- Known condition predisposing the patient to cutaneous neoplasia, i.e. Basal Cell Nevus Syndrome (BCNS) or xeroderma pigmentosum (XP)
- Known exposure to arsenic
- Known skin condition which is likely to require use of topical medications
- Planned pregnancy during the duration of the 5 year study

H. Recruitment Of Subjects

Consecutive patients who are diagnosed with a first occurrence of NMSC by a Columbia University dermatologist will be invited to participate in this study at the time of diagnosis.

I. Confidentiality Of Study Data

Any information obtained from this study and identified with a particular patient will remain confidential.

J. Potential Conflict Of Interest

None.

K. Location Of Study

Columbia Presbyterian Medical Center: Irving Pavilion 12th floor Dermatology office suites.

L. Potential Risks

Potential risks due to participation in this study include adverse effects resulting from oral administration of Celecoxib. Celecoxib has been FDA approved for the treatment of signs and symptoms

of rheumatoid arthritis and osteoarthritis, and for the regression and reduction of adenomatous polyps in familial adenomatous polyposis. In studies conducted by G.D. Searle, the adverse event with the highest incidence was headache, occurring in 25% of the placebo group, 11% of the 400mg BID group, 9% of the 200mg BID group, and 12% of the 400 BID group. Other events reported at more than 8% at 200mg BID included rhinitis, nausea, sinusitis, and upper respiratory infection.

M. Potential Benefits

The potential benefit for the patient is the possible chemopreventive effect of celecoxib. This benefit will only be applicable to those enrolled in the study group. In addition, each participant will receive comprehensive dermatologic exams every 3 months to monitor for recurrence of NMSC. These exams will be provided free of charge for the duration of the 5 year study.

N. Alternative Therapies

Patients may choose not to participate in this study.

O. Compensation To Subjects

None.

P. Costs To Subjects

Patients will not be billed for participation in this study.

Q. Minors As Research Subjects

Not applicable.

R. Radiation Or Radioactive Substances

Not applicable.

S. References

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Figure 1: Study Questionnaire: Initial Evaluation

Celecoxib as Chemopreventive Agent: Initial Evaluation

Name: MRN:
Age:
Sex:

Presenting NMSC:
Diagnosis (Circle one): SCC BCC
Date of Diagnosis:
Location:
Size:
Description:
Date of Excision:

Exclusion Criteria: (Circle one)

Regular use of NSAIDs more than 2 times per week	Y	N
Known hypersensitivity to NSAIDS or COX-2 inhibitors	Y	N
Active gastrointestinal disease precluding COX-2 inhibitor usage	Y	N
Prior diagnosis of a gastrointestinal ulcer	Y	N
Known predisposition to cutaneous neoplasia, (i.e. BCNS, XP)	Y	N
Known exposure to arsenic	Y	N
Known skin condition likely to require use of topical medications	Y	N
Planned pregnancy during the duration of the 5 year study	Y	N

Other considerations:
Fitzpatrick Skin Type (Circle one):
I II III IV V VI
Total number of prior NMSC, including presenting NMSC (Circle one):
1 2 3 4 5 6 7 8 9 >9
Estimated hours of sun exposure per week:
Sunscreen usage frequency:
Sunscreen SPF:

Other Medical Conditions:
Current Medications:

Figure 2: Study Questionnaire: Follow-up Evaluation

Celecoxib as Chemopreventive Agent: Follow-up Evaluation

Name: MRN:
Date:

History:
Estimated number of missed doses:
Pill count:
Adverse effects from therapy:
Estimated hours of sun exposure per week:
Sunscreen usage:

Dermatologic exam:
New NMSC (Do not include recurrence of presenting NMSC):
(Circle one): SCC BCC AK None

If new lesion is present:
Date of Diagnosis:
Location:
Size:
Description:

Other comments: