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A Stratified Randomized Double-Blind Phase II Trial of Celecoxib for Treating Patients with Cervical Intraepithelial Neoplasia: The Potential Predictive Value of VEGF Serum Levels: an NRG Oncology/Gynecologic Oncology Group Study

Janet S. Rader, MD¹, Michael W. Sill, PhD², Jan H. Beumer, Pharm, PhD, DABT³, Heather A. Lankes, PhD MPH², Doris Mangiaracina Benbrook, PhD⁴, Francisco Garcia, MD, MPH⁵, Connie Trimble, MD⁶, J. Tate Thigpen, MD⁷, Richard Lieberman, MD⁸, Rosemary E. Zuna, MD⁹, Charles A. Leath III, MD, MSPH¹⁰, Nick M. Spirtos, MD¹¹, John Byron, MD¹², Premal H. Thaker, MD¹³, Shashikant Lele, MD¹⁴, and David Alberts, MD¹⁵

¹Department of Obstetrics and Gynecology; Medical College of Wisconsin, Milwaukee, WI 53226

²NRG Oncology/Gynecologic Oncology Group Statistics & Data Center; Roswell Park Cancer Institute, Buffalo, NY 14263

³Cancer Therapeutics Program, University of Pittsburgh Cancer Institute; Department of Pharmaceutical Sciences, School of Pharmacy, Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

⁴Department of Obstetrics and Gynecology; University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104

⁵Department of Obstetrics & Gynecology; University of Arizona; Mel & Enid Zuckerman College of Public Health; Tucson, AZ 85724

⁶Division of Gynecologic Specialties; Johns Hopkins Medical Institutions, Baltimore, MD 21287

⁷Department of Gynecologic Oncology; University of Mississippi Medical Center; Jackson, MS 39216

⁸Division of OB/GYN and Pathology, University of Michigan Health System; Ann Arbor, MI 48109

⁹Department of Pathology; University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104

¹⁰Division of Gynecologic Oncology; University of Alabama at Birmingham; Birmingham, AL 35233

¹¹Division of Gynecologic Oncology; Women's Cancer Center of Nevada, Las Vegas, NV 89169

Corresponding author: Janet S. Rader, MD, Department of Obstetrics and Gynecology, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226, Telephone: 414-805-6606, Fax: 414-805-6622, jrader@mcw.edu.

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CONFLICTS OF INTEREST

All other co-authors have no conflicts of interest to declare.

¹²Department of OB/GYN; First Health of the Carolinas – Moore Regional Hospital; Southern Pines, NC 28388

¹³Division of Gynecologic Oncology; Washington University School of Medicine; Saint Louis, MO 63110

¹⁴Department of Gynecologic Oncology; Roswell Park Cancer Institute, Buffalo, NY 14263

¹⁵Department of Medical Oncology; The University of Arizona Cancer Center- North Campus; Tucson, AZ 85724

Abstract

Purpose—To examine the effect of celecoxib on cervical intraepithelial neoplasia 3 (CIN 3).

This is a **NRG Oncology**/Gynecologic Oncology Group study with translational biomarkers.

Patients and Methods—Patients with CIN 3 were randomized to celecoxib 400 mg once daily (67 patients) or placebo (63 patients) for 14–18 weeks. The primary outcome measure was histologic regression. A test of equal probabilities of success between two therapies was conducted, using Fisher's Exact Test at $\alpha=10\%$ and 90% power when the treatment arm boosted the probability of success by 30%. Translational analysis included cervical tissue HPV genotyping, COX-2 expression in biopsies, and serum celecoxib and VEGF levels.

Results—In primary analysis, histologic regression was not significantly higher in the celecoxib group (40%) than in the placebo group (34.1%). However, exploratory analyses suggest patients with high serum VEGF levels exhibited greater regression in the celecoxib arm (47.3%) than in the placebo arm (14.3%). Regression rates were similar by treatment group in patients with low VEGF. VEGF levels increased over time in the placebo group, but remained the same in the treatment group. COX-2 expression in cervical biopsies declined from pre-treatment to the end of treatment with celecoxib; it did not change with placebo.

Conclusions—Celecoxib at 400 mg once daily for 14–18 weeks did not significantly decrease the severity of CIN 3 compared with placebo except, possibly, in subjects with high baseline VEGF. Therefore, serum VEGF levels might identify patients who may benefit from celecoxib or other therapies, personalizing future chemoprevention trials for CIN 3.

Keywords

COX-2; cervix; VEGF; chemoprevention; celecoxib; CIN 3

INTRODUCTION

Cervical cancer is the third-most common malignant disease in women worldwide, with an estimated annual worldwide incidence of 528,000 new cases [1]. Human papillomavirus infection accounts for most cases, and preventive vaccines have been available since 2006. However, vaccination will not prevent the development of cervical cancer in the large number of women already infected with the virus. Therefore, management of pre-invasive cervical lesions remains a challenge.

Women diagnosed with cervical intraepithelial neoplasia 3 (CIN 3) are frequently in their reproductive years, and treatment must preserve fertility in addition to being safe and effective. Today, CIN 3 is most commonly treated with large-loop excision of the transformation zone (LLETZ) or cone excisions of the cervix. These procedures can affect future fertility and by shortening the cervix, increase the risk of preterm delivery [2]. As a result, there has been great interest in pursuing alternative non-surgical treatments for CIN. Trials designed to evaluate the chemopreventive and anti-tumor effects of retinoids, [3] β -carotene, difluoromethylornithine, indole-3-carbinol, cidofovir, imiquimod, and celecoxib, have been undertaken but many of those studies were inconclusive or underpowered [4–9].

Modulation of prostaglandin production is a promising avenue for chemoprevention, as the eicosanoid pathway plays a pivotal role in initiating and promoting cancer, including cervical cancer [10–12]. Many tumors produce large amounts of prostaglandin E₂ (PGE₂) which promotes tumor growth by inhibiting apoptosis, suppressing immune function, and promoting angiogenesis [12]. Cyclooxygenases (COX) are key enzymes in the conversion of arachidonic acid to prostaglandins. Two forms of COX derived from separate genes have been described. COX-1 is expressed constitutively in a wide range of tissues. COX-2 is induced at sites of inflammation and tumors, and its level is elevated in solid tumors [12]. Celecoxib is a selective COX-2 inhibitor with chemopreventive and antitumor effects [13,14]. The Gynecologic Oncology Group (GOG) undertook a stratified randomized phase II trial to examine the toxicity and histologic response to celecoxib in women with CIN 3. As outlined in the initial protocol, the study also examined HPV types, VEGF levels, COX2 levels in serum and cervical tissue and a telepathology protocol for review of samples.

PATIENTS AND METHODS

Patient Selection

Eligible patients included women $\geq$ 18 years with CIN 3 verified by a central pathology review and a lesion visible by colposcopy 2–8 weeks after biopsy. Exclusion criteria included adenocarcinoma-*in-situ* of the cervix, pregnancy, allergies to sulfonamides, history of immunocompromised condition, peptic ulcer disease, TIA, stroke, cardiovascular disease or uncontrolled hypertension, and renal or hepatic disorders. At enrollment, candidates underwent baseline blood work and a physical exam, including colposcopy. A serum sample and cervical swabs were obtained in ThinPrep vials (Hologic, Inc, Marlborough, MA) for research only. Participants received written materials on managing possible gastrointestinal symptoms and instructions on contraception use.

Study Design and Treatments

The primary endpoints of this multicenter, stratified, randomized, double-blind phase II trial ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT- 00081263) were (1) histologic regression to CIN 1 or less, and (2) estimation of the toxicity of celecoxib (400 mg once daily) as assessed by Common Terminology Criteria for Adverse Events (CTCAE) v 3.0. All patients who received any therapy were evaluated for toxicity. Stratified randomization was chosen to help balance treatment assignments by lesion size (coverage $\geq$ 50% or $<$ 50% of the cervix) and severity of CIN (CIN 2/3 or CIN 3). as documented in local institutional pathology reports.

Eligible cases required presence of CIN 3 on central GOG pathology review. All patients received either 1 capsule of celecoxib (400 mg) once daily or a comparable placebo. Celecoxib and placebo were supplied by Biologics Inc. (Cary, NC). Treatment was continued for 14–18 weeks, with an interval safety exam and colposcopy at 8 weeks. No disease progression was identified and no biopsies performed.

Statistical methods

Patients were randomized in a 1:1 fashion to treatment groups called the experimental and placebo regimens. Randomization was stratified by lesion size (≤ 0.5 cervix versus >0.5 cervix) and severity/type (CIN 3 versus CIN 2/3) by local institutional pathology review. However, eligibility required all patients to have CIN 3 identified at central GOG pathology review. The study was designed as a single stage trial with a total accrual of 100 patients, assuming about 20% loss to follow-up. After accruing 101 patients, the study was reopened to accrue 29 additional patients without an interim efficacy analysis because a larger than expected proportion of the original cases were inevaluable or ineligible (Figure 1).

Only patients with normal or squamous metaplasia post-therapy biopsies were deemed to have complete responses while those with CIN 1 were classified as partial responses. Both results were deemed successful outcomes (“responses”). Patients who submitted a post-therapy sample but could not have their tissue evaluated histologically or had adenocarcinoma *in-situ* were deemed to have indeterminate responses. Progressive disease was defined by the identification of squamous cell carcinoma and persistent disease by the presence of CIN 2, CIN 3, or squamous cell carcinoma, *in-situ* after completing therapy.

Treatment response was dichotomized into responses or non-responses. The proportion of patients responding to therapy was compared by treatment arm with odds ratios (experimental to placebo) and Fisher’s exact test. With 40 patients per arm, the study had at least 90% statistical power when the experimental regimen boosted the proportion responding by 30% (e.g., 35% to 65%) when testing the null hypothesis of equal probabilities of response at the 10% level of significance against a 1-sided alternative.

A series of translational studies was performed on samples collected during the study as outlined in the initial protocol and prospectively collected. All biological analyses were blinded to treatment. None of the translational study results were used in the management of patients in this trial. The procedures for determining serum celecoxib and vascular endothelial growth factor (VEGF) levels, human papillomavirus (HPV) typing, COX-2 tissue immunohistochemistry (IHC), telepathology and additional statistical methods can be found in Supplemental Methods. Results are exploratory. When the p-values were < 0.05 and $0.05 < p < 0.10$, the results were considered “suggestive” or “borderline suggestive” respectively due to the large number of tests. Because of relatively small sample sizes, negative results should not be considered definitive.

RESULTS

Patient characteristics

Between June 13, 2005 and April 18, 2012 we enrolled 130 patients. Enrollment was suspended on June 22, 2009, after we accrued 101 patients. In February 2010, the proportion of eligible and evaluable patients was estimated to be close to 60% instead of the anticipated 80%. Therefore, the accrual target was revised to 130 patients in total (29 more patients than initially planned), and enrollment was reopened on September 27, 2010. Accrual goals were reached with 91 eligible and evaluable subjects whose baseline demographic, clinical, and pathologic features are listed in Table 1 and study flow diagram Fig 1.

Adverse events

Adverse events, mostly mild and infrequent, were evaluable in 121 women (Table 2). There was one grade 3 gastrointestinal toxicity in the celecoxib group, but grades 1 and 2 toxicity was similar in the placebo and celecoxib groups. The relative risk for pain (grades ≥ 1 ; celecoxib to placebo) was 0.54 with a 95% CI 0.27 to 1.09..

Activity of Celecoxib

Histologic endpoints were assessed in 91 women eligible for response to treatment (Table 3): 50 in the celecoxib arm and 41 in the placebo arm. The proportion of patients with histologic responses was 20/50 (40%) in the celecoxib group and 14/41 (34.1%) in the placebo group (one-sided Fisher's exact test $p=0.36$). The odds ratio of responding in the celecoxib arm to the placebo arm was estimated at 1.28 (90% 2-sided CI 0.57 ~ 2.89). No subjects progressed to invasive cancer. Using an intent to treat analysis of all enrolled patients, the proportion of patients with histologic responses was 20/67 (29.9%) in the celecoxib group and 14/63 (22.2%) in the placebo group (one-sided Fisher's exact test $p=0.22$). The odds ratio of responding in the celecoxib arm to the placebo arm was estimated at 1.49 (90% 2-sided CI 0.63 ~ 3.58). Lesion area at initial colposcopy (less than or greater than 50%) was not associated with response (FET, $p=0.74$), though only 10 patients had lesion area $>50\%$. Responses at 14–18 weeks were identified in 31/81 (38%) of women with lesion areas of $\leq 50\%$ and 3/10 (30%) of women with lesion areas of $>50\%$.

Serum samples for celecoxib concentration were collected at 8 weeks and were available from 79 patients who were eligible and evaluable for response (45 in the celecoxib group and 34 in the placebo group). At 14–18 weeks, 76 serum samples (41 celecoxib, 35 placebos) were collected and evaluated. Two patients assigned to celecoxib had no detectable drug at both time points. Serum levels for concentrations ≥ 30 ng/mL ranged from 36.8 to 2455 ng/ml (median 341 ng/ml) at 8 weeks, and 40.5 to 1856 ng/ml (median 300 ng/ml) at 14–18 weeks. Using the 8-week time point and the presence or absence of celecoxib in our analysis, we obtained a response rate of 46% when celecoxib was present and 33% when it was not (Fisher's exact test 1-sided $p=0.18$) (Table 4).

Patients recorded daily pill use, and any returned pills were counted at the 8 and 14–18 week visits to assess adherence to oral medication. According to institutional pill counts from returned bottles, the median percentage of pills expected to be consumed was 88% (range

10% – 125%) during the first period.. A number greater than 100% means the patient consumed more than what was directed. The median percentage of pills expected to be consumed was 99% for the second period (week 8 to week 14–18).. The range was 14% to 200% (twice the directed dosage). The diary entries and pill counts correlated very well at the midpoint and final visits (Spearman's $r_s = 0.96$ and $r_s = 0.56$, respectively) for the celecoxib group (diary counts were not abstracted for the placebo group).

COX-2 IHC

Histological data were available for 85 of the 91 evaluable patients: 72 at enrollment and 66 at the end of treatment. The epithelium of the highest-grade lesion on a slide was scored. There was a general trend for the stroma to match the epithelium (i.e., when the epithelium was strongly positive, the stroma was also strongly positive, and vice versa) (Figure S1, Table S1). The distribution of COX-2 IHC staining in the cervical CIN epithelium in those randomized to celecoxib and placebo was similar before treatment. There was a suggestive decline in COX-2 expression from pre-treatment to the end of treatment in the celecoxib group (40 point H-score decline; $p=0.04$). There was no association between COX-2 level and response in either group.

VEGF serum levels

Serum VEGF levels were evaluated before treatment and at 8 and 14–18 weeks. The subset analysis was borderline suggestive for an increase over time in the placebo group by the 14–18 week visit (26 pg/ml) but appeared to remain the same in the celecoxib group at both week 8 (increased by 13 pg/ml) and weeks 14–18 (decreased by 3.3 pg/ml) (Figure S2, Table S1). Individuals were categorized as having high or low serum VEGF if their pre-treatment levels were above or below the median (106 pg/ml), respectively. Before treatment, serum from 80 patients was available for VEGF analysis. There were no differences in response between the treatment and placebo groups for patients with low VEGF levels, with a 33.3% response for celecoxib and a 43.8% response for placebo. Patients with high VEGF levels, however, exhibited a greater response with 47.3% in the celecoxib arm in comparison to the 14.3% proportion responding in the placebo group (Subset *OR* for responding in celecoxib arm to placebo arm is 5.4, 95% CI 1.18 ~ 24.63 within the high VEGF group versus *OR*=0.64, 95% CI 0.17 ~ 2.36 in the low VEGF group) (Table 5). An interaction term between treatment and VEGF level using logistic regression was suggestive, indicating that the ratio of the odds ratio for response was 8.4, 95% CI 1.14 ~ 62.1. Zelen's exact test for homogeneity of odds ratios was also suggestive against equal odds ratios.

There was no association between pre-treatment COX-2 levels in cervical tissue and VEGF levels in serum (Spearman correlation: $r=-0.083$, 95% CI $-0.34 \sim 0.17$, $n=63$ for both arms and $r=-0.208$, 95% CI $-0.55 \sim 0.13$, $n=34$ for the celecoxib arm). However, a negative but weak association was suggested between pre-treatment COX-2 levels and the degree of VEGF changes when comparing pre-treatment samples with either week 8 or week 14–18 samples (Spearman correlation: $r=-0.299$, 95% CI $-0.55 \sim -0.05$, $n=56$, and $r=-0.326$, 95% CI $-0.59 \sim -0.06$, $n=54$, respectively) (Figure S3).

HPV typing

Cervical swab samples obtained at enrollment were available for 82 of the 89 subjects who were eligible and evaluable for HPV typing; those obtained when the study ended were eligible and evaluable for 71 of 82 subjects. Of the 71, 67 provided samples at both time points. The DNA in 8 samples could not be analyzed because of its poor quality. In the pre-treatment samples, the median number of different HPV types per sample was 2; the range was 0–6. HPV 16 was the most prevalent, as it was detectable in 84% (69/82) of the samples collected at enrollment and 77% (55/71) of those obtained at completion. Five of the 13 (38.5%) subjects who were HPV 16-negative at enrollment responded to celecoxib, and 25 of the 69 (36.2%) who were HPV 16-positive also responded (OR of responding among HPV16+ to HPV16– was 0.909, 95% CI 0.268 ~ 3.081).

Telepathology

Three pathologists remotely read the scanned histologic slides from subjects enrolled onto the study. The weighted kappa for the three comparisons between each pair of pathologists, where both rated the severity of CIN as either normal, CIN 1, CIN 2, or CIN 3, ranged from 0.56 to 0.62. The weighted kappa for CIN severity (pathologic eligibility criteria) for the 48 subjects was 0.5294, 95% CI 0.1368~0.9220 when the consensus of the 3 pathologists was compared to the GOG central pathology review.

DISCUSSION

Daily treatment of women with CIN 3 with 400 mg of celecoxib was very safe in our study. However, it did not achieve the primary endpoint of efficacy. The proportion with histologic response was 40% in the celecoxib group — not significantly greater than the 34.2% in the placebo group. Both groups had pathologic confirmation of CIN 3 and a persistent lesion on the cervix weeks after the diagnostic biopsy.

Women with high initial serum VEGF levels, defined by levels above the median, were more likely to have a greater histologic response to celecoxib (47.4%) than to placebo (14.3%). The proportion responding to celecoxib or placebo was about equal in the low VEGF group (~38%) (Table 5). We therefore identified serum VEGF as a potential predictive biomarker for future investigation where high VEGF could indicate greater disease persistence without celecoxib treatment.

Other studies have shown that COX-2 inhibition may be mediated partially through inhibition of VEGF production. COX-2 expression leads to an increase in PGE₂, a powerful angiogenic mediator, and VEGF is one of the most important inducers of angiogenesis. Derosa *et al.* reported that high plasma VEGF levels and single nucleotide polymorphisms (SNPs) in the *VEGFA* gene predicted the response of castrate-resistant prostate cancer patients to metronomic cyclophosphamide and celecoxib chemotherapy [15]. This is not unexpected, as celecoxib inhibits VEGF expression through SP1-binding sites in the *VEGFA* gene promoter and reduces VEGF levels in various murine carcinogenesis models [16–19]. *In vitro* studies and clinical trials of COX-2 inhibition have observed significant reductions in VEGF levels when COX-2 levels are high [20,21]. After celecoxib and

radiation were used to treat head and neck cancers, only patients with high COX-2 had significantly lower serum VEGF levels [20]. Moreover, the baseline ratio of COX-2 to 15-hydroxyprostaglandin dehydrogenase mRNA (an indication of increased PGE2) in bronchioalveolar lavage cells predicted response to celecoxib in a lung cancer prevention study [22]. These studies suggest that a population of tumors across several cancer sites have an inflammatory-angiogenic phenotype. Indeed, neovascularization of the cervix is the hallmark of a CIN diagnosis by colposcopic examination. In addition, microarray gene expression and IHC studies show increased VEGF and angiogenesis along the basement membrane of pre-invasive lesions in human cervical tissues and a transgenic mouse model of cervical cancer [23–27].

Two randomized trials of COX-2 inhibitors in CIN have been published. One study randomized 25 women to 200 mg of celecoxib twice daily for 6 months versus placebo [9]. The second randomized 16 women to 25 mg of rofecoxib once daily for 3 months versus placebo [28]. The second study was discontinued early when rofecoxib was withdrawn from the market in 2004. However, the combined results from both studies show that CIN 2 or 3 partially or completely regressed in 11 of 20 (55%) women in the treatment arms and only 5 of 21 (23.8%) in the placebo arm ($p=0.04$; 95% risk ratio 2.35, CI 1.03 to 5.35) [9,28,29].

Several possible explanations might account for the ineffectiveness of celecoxib in our study. One could be noncompliance with the treatment regimen. This scenario seems unlikely, as we documented compliance both indirectly (with pill counts and diaries) and directly (by measuring celecoxib levels in serum). The indirect methods correlated highly with each other. Also, subjects' acceptance of the drug's side effects did not appear to be a major problem.

Our choice of dosage and schedule might also have been a factor. The plasma half-life of celecoxib is 8–12 hours, but pharmacology as expressed by side-effects varies by dosage and schedule [30]. In a group of volunteers using 200 mg celecoxib twice daily for 15 days, the mean peak level was 900 ng/mL at 2.5 hours from last dose, >200 ng/mL at 12 hours, and >100 ng/mL at 24 hours [31]. In another group using 400 mg celecoxib once daily for 6 weeks, the mean level was 600 ng/mL at 13 hours from the last dose [32]. In a study of women at high risk for breast cancer, a significant decrease in levels of PGE2 in nipple aspirate fluid occurred in women taking 400 mg celecoxib twice daily for 2 weeks, where the median circulating concentration of celecoxib was 860 ng/mL. There was no significant decrease in PGE2 in women taking 200 mg twice daily, where the median circulating concentration was <300 ng/mL [33]. Other studies with variable celecoxib doses and durations have shown improved endpoints with higher doses and longer durations [13,14,34–36]. Thus in our study, 400 mg twice daily might have provided more therapeutic benefit than a once-daily dose.

The trial was originally designed to use 400 mg twice daily dosing, but on December 17, 2004, the National Cancer Institute suspended celecoxib use for all participants in the Adenoma Prevention with Celecoxib (APC) trial because an independent Data Safety and Monitoring Board found an increased risk of fatal and non-fatal cardiovascular events at 200 mg and 400 mg twice daily. There was no increased risk in the Prevention of Colorectal

Sporadic Adenomatous Polyps (PreSAP) trial at 400 mg once daily [30]. In January 2005, just before our trial began, we decreased the dose to 400 mg once daily and added exclusion criteria for cardiovascular risks. Our resulting study had few side effects, probably due to its short (14–18 weeks) treatment duration, once daily dosing, and young participants (mean age <30 years compared to ~60 years in colorectal cancer prevention trials).

Histologic confirmation was also problematic in our study due to discrepancies in pathologic grading and interpretation and the time taken for GOG central pathology to verify the diagnoses of the local site pathologists. A quicker review would have allowed us to verify eligibility more promptly to decrease the time and cost of enrolling and treating ineligible patients (10% in this study). A move toward a two-tier system of low and high grading, with high-grade intraepithelial lesions encompassing CIN 2 and CIN 3/carcinoma *in situ*, [38] would also make histologic diagnosis more reproducible. However, if CIN 2 were included with CIN 3 as high-grade disease, the spontaneous regression rate would be even higher than the 34% seen in this study. In addition to correctly selecting subjects, scanning whole slides would improve turnaround time for verification of eligibility by allowing for expedited on-line confirmation of entry diagnosis of the same histologic section without having to ship slides to multiple locations, decreasing the chance that the histologic characteristics of a lesion may be different on the new slides.

In summary, this study provides important clinical and molecular information for the design of personalized chemoprevention trials for women with CIN 3. Focusing enrollment on women with CIN 3, who would be less likely to undergo spontaneous regression, would diminish the expense and complexity of chemoprevention trials. Serum VEGF levels should be explored, as more than 86% of the women with high serum VEGF levels in our placebo group had persistent disease. Serum VEGF could also provide a baseline and serial surrogate biomarker that would not require cervical biopsy. Future studies of celecoxib might also consider extending treatment beyond 14–18 weeks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Table 1

Characteristics of eligible and evaluable women enrolled in GOG 0207

Characteristic	Total	Celecoxib No. (%)	Placebo No. (%)
Total eligible patients	91	50	41
Age group			
18–19	6	1 (2%)	5 (12%)
20–29	53	30 (60%)	23 (56%)
30–39	23	13 (26%)	10 (24%)
40–49	9	6 (12%)	3 (7%)
Ethnicity			
Hispanic	28	16 (32%)	12 (29%)
Non-Hispanic	60	33 (66%)	27 (66%)
Unknown	3	1 (2%)	2 (5%)
Race			
Caucasian	75	42 (84%)	33 (81%)
African American	6	3 (6%)	3 (7%)
American Indian	1	1 (2%)	0 (0%)
Asian	2	1 (2%)	1 (2%)
Pacific Islander	2	0 (0%)	2 (5%)
Unspecified	5	3 (6%)	2 (5%)
Performance status			
0	89	49 (98%)	40 (98%)
1	2	1 (2%)	1 (2%)
Baseline institutional pathology			
CIN 2/3	25	14 (28%)	11 (27%)
CIN 3	66	36 (72%)	30 (73%)
Colposcopy lesion size			
50%	81	44 (88%)	37 (90%)
> 50%	10	6 (12%)	4 (10%)
HPV type (82 samples)*			
HPV positive (1 or more HPV infections)	80	43 (96%)	37 (100%)
HPV 16	69	35 (78%)	34 (92%)
HPV 18	3	1 (2%)	2 (5%)
HPV 45	1	1 (2%)	0 (0%)
Total	82	45	37

* Some samples had more than 1 HPV type

Table 2

Adverse events

Adverse Event Category	Treatment Group	0	1	2	3	4	5	Total
Anemia	Celecoxib	62	1	0	0	0	0	63
	Placebo	58	0	0	0	0	0	58
Constitutional	Celecoxib	61	2	0	0	0	0	63
	Placebo	54	3	1	0	0	0	58
Dermatologic	Celecoxib	63	0	0	0	0	0	63
	Placebo	57	0	1	0	0	0	58
Gastrointestinal	Celecoxib	51	7	4	1	0	0	63
	Placebo	44	11	3	0	0	0	58
Genitourinary/Renal	Celecoxib	63	0	0	0	0	0	63
	Placebo	57	1	0	0	0	0	58
Hemorrhage	Celecoxib	62	0	1	0	0	0	63
	Placebo	56	2	0	0	0	0	58
Infection	Celecoxib	62	0	1	0	0	0	63
	Placebo	56	0	1	1	0	0	58
Lymphatics	Celecoxib	60	2	1	0	0	0	63
	Placebo	55	3	0	0	0	0	58
Neurological [†]	Celecoxib	63	0	0	0	0	0	63
	Placebo	54	2	2	0	0	0	58
Ocular/Visual	Celecoxib	62	1	0	0	0	0	63
	Placebo	57	1	0	0	0	0	58
Pain	Celecoxib	53	10	0	0	0	0	63
	Placebo	41	15	1	1	0	0	58
Sexual/Reproductive	Celecoxib	63	0	0	0	0	0	63
	Placebo	57	1	0	0	0	0	58

Common Toxicity (CTC) version 3.0

[†]The data suggested that a greater proportion of people on the placebo treatment had neurological symptoms. These included dizziness, somnolence, and involuntary movement. No other associations were suggested.

Table 3

Primary analysis endpoint

Characteristic	Category	Total (%)	Celecoxib No. (%)	Placebo No. (%)
Histologic response	Complete Response	19 (20.9)	11 (22.0)	8 (19.5)
	Partial Response	15 (16.5)	9 (18.0)	6 (14.6)
	Persistent Disease	55 (60.4)	30 (60.0)	25 (61.0)
	Indeterminate	2 (2.2)	0	2 (4.9)
Histologic response	No Response	57 (62.6)	30 (60.0)	27 (65.9)
	Complete, Partial Response *	34 (37.4)	20 (40.0)	14 (34.1)
Total		91	50 (54.9)	41 (45.1)

Complete response – no CIN; Partial response – CIN 1, viral changes present

The maximum likelihood estimate of the odds ratio for histological response (celecoxib to placebo) is 1.28 with a 90% CI 0.57 ~ 2.89.

One sided p-value was 0.36 for H_a : $OR > 1$.

* The 90% CI for response in the celecoxib arm was 28.3 ~ 52.6%.

* The 90% CI for response in the placebo arm was 22.0 ~ 48.1%.

Table 4

Histologic responses by presence of quantifiable serum celecoxib

	Histologic response		Total
	No response	Complete and partial response	
8 week serum celecoxib			
Present	20	17 (46.0%)	37
Undetectable	28	14 (33.3%)	42
Not available	9	3 (25.0%)	12
14–18 week serum celecoxib			
Present	23	15 (39.5%)	38
Undetectable	25	13 (34.2%)	38
Not Available	9	6 (40.0%)	15
8 and 14–18 week serum celecoxib			
Present	16	12 (42.9%)	28
Undetectable	26	16 (38.1%)	42
Not available	15	6 (28.6%)	21
Total			

Complete response – no CIN; Partial response – CIN1, viral changes present

Limit of quantitation (LOQ) was 30 ng/mL

Table 5

Histologic responses by serum VEGF levels

	Celecoxib n (%)	Placebo n (%)	Total
Low VEGF group			
CR + PR	8 (33.3%)	7 (43.8%)	15
No response	16 (66.7%)	9 (56.3%)	25
High VEGF group			
CR + PR	9 (47.4%)	3 (14.3%)	12
No response	10 (52.6%)	18 (85.7%)	28

Complete response (CR) – no CIN; Partial response (PR) – CIN1, viral changes present Zelen's Exact Test suggested different odds ratios for response (treatment to placebo) by VEGF; low VEGF OR=0.64 and high VEGF OR=5.4. The ratio of the odds ratio for response was 8.4 (95% CI 1.14 ~ 62.1), based on a logistic regression interaction term.