The Efficacy of 9-Cis-Retinoic Acid (Aliretinoin) as a Chemopreventive Agent for Cervical Dysplasia: Results of a Randomized Double-Blind Clinical Trial


Abstract

9-Cis-retinoic acid (aliretinoin) is a pan-retinoid receptor agonist and has been demonstrated in preclinical models to have potent chemoprevention effects. The purpose of this study was to determine the utility of using aliretinoin as a chemoprevention agent in cervical dysplasia.

Patients with histological evidence of cervical intraepithelial neoplasia (CIN) 2/3 were randomized in a double-blind manner to receive high-dose aliretinoin (50 mg), low-dose of aliretinoin (25 mg), or placebo daily for 12 weeks. Compliance and side effects were monitored at various time points during therapy. At the completion of therapy, all of the patients underwent a loop procedure. Histology of pretreatment biopsies was compared with that of loop specimens.

One-hundred and fourteen patients with CIN 2/3 were enrolled in the study. In the 112 patients evaluable for toxicity, headache was the most common clinical side effect and was experienced more frequently (74%) in the high-dose aliretinoin group. Eight patients withdrew from the study before completion of study medication because of unacceptable side effects. In the 104 patients evaluable for efficacy, there was no statistical difference in the rate of regression among the placebo (32%), the low-dose aliretinoin (32%), and the high-dose aliretinoin (36%) groups. (P = not significant; power 0.06).

Aliretinoin at these dosages and this schedule does not appear to result in significant regression rates in CIN 2/3 patients when compared with placebo. Headache is encountered frequently and may thwart efforts to increase the dose or duration of aliretinoin in future cervical cancer chemoprevention studies. The rate of histological regression in biopsied CIN 2/3 patients is high even over a short time interval, and emphasizes the importance of having a placebo arm and an adequate sample size in cervical dysplasia chemoprevention studies.

Introduction

Chemoprevention refers to the use of natural or pharmaceutical compounds with low toxicity to suppress or reverse the mechanisms involved with carcinogenesis. Retinoids have been investigated as a chemoprevention strategy for various organ site cancers including cervical neoplasia, one of the leading causes of cancer mortality for women worldwide (1). Retinoids are required for the maintenance of normal epithelial cell growth, differentiation, and cellular death, and they exert their activity via their interaction with retinoid receptors, which are members of the steroid receptor superfamily (2). Studies have demonstrated that retinoid receptors are present in normal, dysplastic, and malignant cervical tissue (3–5). Various retinoids have been demonstrated to inhibit cellular proliferation in cervical cancer cells in several studies, thereby justifying investigation of these agents as potential chemoprevention agents for cervical cancer (6–8).

The retinoids used in chemoprevention trials for cervical and other neoplasms have included those that interact predominantly with RAR retinoid receptors. 9-Cis-retinoic acid (aliretinoin) binds not only to RAR retinoid receptors but also to RXR retinoid receptors (9). This “pan-agonist” retinoid has been demonstrated to inhibit HPV E6/E7 transcription and to exert antiproliferative effects in cervical squamous cancer cells in vitro (10, 11). Thus, we report the results of a placebo-controlled, double-blinded trial investigating the efficacy of aliretinoin as a chemopreventive agent for patients with CIN3 2/3.

Materials and Methods

Patient Eligibility Criteria. Patients were recruited to participate in this study from the Colposcopy Clinic and Gynecologic Oncology practice at the University of Alabama at Birmingham. Patients age 18 or greater were deemed eligible if they had histological confirmation of CIN 2 or CIN 3, and had a visible dysplastic lesion occupying at least one quadrant of the ectocervix. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0, 1, or 2, and have

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3 The abbreviations used are: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HDL, high-density lipoprotein; NS, not significant; ATRA, all-trans-retinoic acid; 4-HPR, 4-hydroxy-phenylretinamide.
normal organ function defined as a WBC >3,500/mm³, a platelet count >125,000/mm³, total bilirubin <2.0 mg/dl, aspartate aminotransferase and alanine aminotransferase <2 times upper limits of institutional normal, and serum creatinine <2.0 mg/dl. Patients also were required to have a total cholesterol level <300 mg/dl and a triglyceride level <200 mg/dl.

Given the potential for teratogenicity, all of the patients also were required to use hormonal or barrier methods of birth control, or to have had a previous tubal ligation. All of the patients were required to have a negative pregnancy test within 7 days of initiating study medication. All of the patients had provided signed informed consent. This study was approved by the University of Alabama at Birmingham Institutional Review Board.

Patients who were pregnant or actively trying to conceive were excluded from the study. Patients with colposcopic evidence of dysplasia extending onto the vagina, disease not amenable to treatment with loop, or invasive cancer were not eligible for this study. Current use of other retinoid class drugs, either topically or systemically, excluded patients from this study. Patients with a history of malignancy other than basal cell carcinoma of the skin also were excluded from the study. Patients with a history of severe migraine headaches, photosensitivity, pancreatitis, or severe depression were ineligible for this study. Patients on lipid-reducing medications were not eligible to participate. All of the study patients were compensated for their time involved with the study and were informed of their right to discontinue participation in the study at any time.

**Treatment Plan.** All of the potential study participants underwent pretreatment history and physical, colposcopic evaluation of the cervix and biopsy (if not performed previously), and assessment of pretreatment laboratories. Once deemed eligible and enrolled onto the study, patients were randomized according to a computer-generated blocked randomization schema to receive a placebo, a low dose (25 mg) of aliretinoin, or a high dose (50 mg) of aliretinoin administered p.o. daily for a total of 12 weeks. These dosages were chosen based on the toxicity profile experienced in Phase I trials of aliretinoin in patients with recurrent cancer detailed in the Investigator’s Drug Brochure provided by Ligand Pharmaceuticals, Inc., and based on pill formulation. Specifically, at aliretinoin dosages >83 mg/m², 58% of patients in these early clinical trials experienced headache, 21% experienced asthenia, 26% experienced nausea, 24% experienced vasodilation, 34% experienced dry skin, and 21% experienced myalgia. We used lower dosages of aliretinoin in an effort to reduce risk of side effects to a minimum, particularly given the ease of treating CIN 2/3 in this patient population. The oral formulation was chosen based on ease of administration over topical applications, consideration of patient compliance, and drug availability.

Medications were preconfigured by the study pharmacist in a blister pack for patients to p.o. self-administer two pills per day. These blister packs contained two placebo pills for patients in the placebo arm, a 25-mg tablet of aliretinoin, and a placebo tablet for patients in the low-dose aliretinoin arm, and two 25 mg tablets for patients in the high-dose aliretinoin arm. All of the pills were identical, thus ensuring that both patients and the study investigators were blinded with respect to which treatment arm an individual patient was randomized. Placebo and aliretinoin pills were provided by Ligand, Inc., and the National Cancer Institute. A 6-week dose of study medication was provided at the initiation of study and at the week 6 evaluation.

**Assessment of Compliance.** Compliance was determined by assessing adherence to scheduled evaluations and to prescribed medication dosing. Patients were provided a daily log and instructed to keep a diary of drug administration. Patients were also instructed to return all of the blister packs and unused medication. Residual pill counts were performed at the week 6 and 12 evaluations after initiation of study medication.

**Evaluation of Toxicity and Safety.** All of the study patients were evaluated for toxicity at week 6 and week 12 by physical examination and laboratory assessment. The study coordinator also contacted each patient by telephone at week 3 and week 9 to assure no untoward interim clinical side effects. Clinical and laboratory toxicity was graded using standard National Cancer Institute Common Toxicity Criteria. The relationship of experienced side effects to study medication was designated as definitely, probably, unlikely, or not related by the principal investigator and study coordinator after questioning and examining each patient. All of the investigators and all of the patients were blinded with regard to assigned treatment at the time toxicity was assessed and relationship to study medication was assigned.

Patients who experienced untoward grade 3/4 clinical symptoms or grade 3/4 laboratory toxicity had a dose reduction of one pill per day (one placebo pill in placebo group or one aliretinoin pill in low-dose or high-dose groups) for a total of 1 week. If this dose reduction did not ameliorate symptoms or toxicity, study drug was discontinued for 1 week. If symptoms did not resolve with discontinuation of drug for 1 week, the study medication was not resumed, and patients underwent a loop. If symptoms resolved with a dose reduction or discontinuation of drug for 1 week, patients resumed study medication as initially prescribed. Patients who subsequently experienced similar and/or unacceptable symptoms or toxicity were removed from the study and had loop performed.

A pap smear and colposcopic evaluation was performed at week 6 to ensure that no patient had progression to invasive cancer. All of the patients with cytologic or colposcopic evidence of invasive carcinoma were removed from the study, and underwent appropriate evaluation and/or treatment. At week 12 (or sooner for patients who experienced untoward symptoms or elected to withdraw from the study), all of the patients underwent loop. This was performed after colposcopic evaluation of the cervix and application of Lugol’s solution for the initial 23 patients or acetic acid for all of the subsequent patients.

All of the patients were evaluated by physical examination, pap smear, and colposcopic examination 3 months after loop to assess for persistent or late drug, or procedure-related toxicity and for persistence of dysplasia.

**Assessment of Effect on Histology.** Histological findings in the pretreatment biopsy were compared with histological findings in the loop specimen. Regressive disease was designated as a reduction in the severity of histological findings between the pretreatment biopsy and loop specimen by at least one degree (i.e., CIN 3 to ≤ CIN 2, CIN 2 to ≤ CIN 1). Progressive disease was defined as an increase in the severity of histological findings between the pretreatment biopsy and loop specimen by at least one degree (i.e., CIN 3 to ≥ MIV, CIN 2 to ≥ CIN 3). Stable disease was designated when there was no change in the severity of histological findings between the pretreatment biopsy and loop specimen.

**Statistical Considerations and Analysis.** Evaluation of the proportion of patients who exhibited histological regression to a lesser grade of dysplasia or complete resolution of dysplasia was one of the primary endpoints of the study. Sample size was
calculated based on the assumptions that no more than 5% of patients would spontaneuously regress to one lesser grade of dysplasia and that at least 35% of patients in each of the aliretinoin arms (moderate effect size = 0.33) would exhibit regression. This would ensure at least 80% power to detect these differences in proportions among the three treatment groups with an $\alpha = 0.05$.

Descriptive statistics including mean, median, SD, SE of mean, and proportion were calculated to summarize patient demographics and clinical characteristics by treatment group. ANOVA was used to compare patient age, whereas the Kruskal-Wallis test was used to compare residual pill counts and laboratory values across the three groups. The change in laboratory values from baseline to 6 and 12 weeks of follow-up within each treatment group was evaluated using the Wilcoxon signed-rank test. Regression rates were summarized for each group and compared using the $\chi^2$ test. Finally, adverse events were summarized by calculating the proportion of specific adverse events among the three groups and were likewise compared using the $\chi^2$ or Fisher’s exact test.

**Results**

**Patient Characteristics and Evaluability.** Between June 1998 and March 2001, 308 patients were screened by telephone or by clinical evaluation. Of the 308 patients screened, 114 patients (37%) consented to participate in this study. Patient demographics are provided in Table 1. There were no statistical differences in patient age, race, weight, height, and current or past habits (tobacco, alcohol, or illicit drug use) among the treatment groups. There was a slight but statistically significant difference in the number of patients with a history of gastro-intestinal disorders in the placebo group (13%) compared with the low-dose (0%) and high-dose (3%) treatment groups ($P = 0.046$). There were also no clinically significant differences in baseline hematologic and chemistry laboratory results among the treatment groups.

There was a statistically significant difference in the number of patients with CIN 3 relative to the number of patients with CIN 2 in the high-dose aliretinoin group in comparison with the other treatment groups (Table 1). This difference was of marginal significance when analyzing the distribution of CIN 2 and 3 in patients included in analysis of efficacy ($P = 0.055$).

Two patients randomized to the high-dose aliretinoin arm did not initiate drug and, thus, were excluded from the analysis of toxicity and efficacy. One patient in the placebo arm, 4 patients in the low-dose aliretinoin arm, and 3 additional patients in the high-dose aliretinoin arm electively withdrew from the study after initiating study medication and did not have a loop procedure performed. These patients were also excluded from the analysis of efficacy in this study. Thus, there were 112 patients included in the analysis of toxicity (38 in placebo arm, 38 in low-dose aliretinoin arm, and 36 in high-dose aliretinoin arm) and 104 patients included in the analysis of efficacy (37 in placebo arm, 34 in low-dose aliretinoin arm, and 33 in high-dose aliretinoin arm).

**Patient Toxicity.** There was a variety of mild to moderate nonspecific symptoms experienced in 86% of the 112 patients assessable for toxicity. The most frequent symptoms were headache (60%), fatigue (31%), and nausea (25%). Although there was no statistical difference in the rate of clinical symptoms among the treatment groups, patients in the high-dose aliretinoin group (74%) experienced headaches more frequently than patients in the low-dose aliretinoin (47%) and placebo (57%) groups ($P = 0.062$). Of the 6 aliretinoin-treated patients who experienced severe headaches, most were ameliorated with a dose modification and analgesics, and only 1 patient with severe headaches withdrew. The relationship of experienced side effects was designated as “probably” associated with study

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**Table 1** Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo ($n = 38$)</th>
<th>Low-dose aliretinoin ($n = 38$)</th>
<th>High-dose aliretinoin ($n = 38$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.5 ± 6.4</td>
<td>25.6 ± 5.7</td>
<td>27.1 ± 5.9</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>24.5 (18–40)</td>
<td>24.5 (18–39)</td>
<td>26 (18–41)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>68%</td>
<td>68%</td>
<td>74%</td>
<td>NS</td>
</tr>
<tr>
<td>African-American</td>
<td>29%</td>
<td>29%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
<td>3%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Weight (lbs.)</td>
<td>151.8 ± 35.5</td>
<td>147.5 ± 40</td>
<td>166.2 ± 44.7</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>146 (96–236)</td>
<td>136 (86–234)</td>
<td>160 (104–277)</td>
<td></td>
</tr>
<tr>
<td>Height (inches)</td>
<td>63.9 ± 2.7</td>
<td>64.9 ± 2.6</td>
<td>64.5 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Median (range)</td>
<td>64 (56–68)</td>
<td>65 (58–71)</td>
<td>65 (59–71)</td>
<td></td>
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<tr>
<td>Pretreatment biopsy (all patients enrolled)</td>
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<td></td>
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<tr>
<td>CIN 2</td>
<td>15 (39%)</td>
<td>21 (55%)</td>
<td>9 (24%)</td>
<td>0.019</td>
</tr>
<tr>
<td>CIN 3</td>
<td>23 (61%)</td>
<td>17 (45%)</td>
<td>29 (76%)</td>
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<tr>
<td>CIN 2</td>
<td>15 (41%)</td>
<td>18 (53%)</td>
<td>8 (24%)</td>
<td>0.055</td>
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<tr>
<td>CIN 3</td>
<td>22 (59%)</td>
<td>16 (47%)</td>
<td>25 (76%)</td>
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</table>
medication more frequently in the high-dose aliretinoin patients (34%) compared with that seen in the low-dose aliretinoin (21%) and placebo (7%) treated patients ($P < 0.0001$).

Baseline, and week 6 and week 12 mean and median values of selected laboratory parameters are demonstrated in Table 2. The reduction in hemoglobin values from baseline to the 6- and 12-week evaluation points for patients in both aliretinoin-treated groups (approximately 0.4–0.55 g/dl in mean value) was statistically larger when compared with the changes in hemoglobin values over time in placebo-treated patients (~0.1 g/dl in mean value; $P = 0.0003$). The change in hemoglobin levels was not of any clinical significance. A statistically significant elevation in median serum triglycerides was noted in both low-dose aliretinoin-treated patients (week 6, $P = 0.0032$; week 12, $P = 0.02$) and in high-dose aliretinoin-treated patients (week 6, $P = 0.011$; week 12, $P = 0.027$). A statistically significant reduction in median HDL levels was also noted in both low-dose aliretinoin-treated patients (week 6, $P = 0.0033$; week 12, $P < 0.0001$) and in the high-dose aliretinoin-treated arm (week 6, $P < 0.0001$; week 12, $P = 0.0045$). These findings were not statistically significant when compared with placebo-treated patients, although no specific effects on triglyceride or HDL levels were noted in this group. Of note, no adverse clinical effects were attributed to any specific alteration in a laboratory parameter in both placebo- and aliretinoin-treated patients.

**Effect on Histology.** Severity of dysplasia was compared between the pretreatment biopsy and the loop specimen. There was no statistically significant difference in the overall rates of regression among the treatment groups (Table 3). Overall, 32% of patients in the placebo group, 32% in the low-dose aliretinoin group, and 36% in the high-dose aliretinoin group had evidence of regression on histological evaluation of the loop specimen ($P = NS$). Histological regression to CIN 1 or less occurred in 22% of patients in placebo group, 24% of patients in low-dose aliretinoin group, and 27% of patients in high-dose aliretinoin group. Analysis of regression by two or more grades of dysplasia demonstrated no significant difference among the treatment groups; there was also no significant difference in histological regression between all of the aliretinoin-treated patients and the placebo-treated patients (data not shown).

Of the 41 patients with CIN 2, 20% in the placebo group, 33% in the low-dose aliretinoin group, and 50% in the high-dose aliretinoin group had regression ($P = 0.349$). Of the 63 patients with CIN 3, 41% in the placebo arm, 31% in the low-dose aliretinoin group, and 32% in the high-dose aliretinoin group had regression ($P = NS$). Progression to a higher degree of dysplasia occurred in 22% of placebo-treated patients, 24% of low-dose aliretinoin-treated group, and 6% of high-dose aliretinoin group ($P = 0.116$). No patient progressed to invasive cancer while on study.

**Discussion**

For nearly 2 decades, retinoids have been investigated as potential chemopreventive agents for cervical dysplasia. A series of early Phase II/III trials (Table 4) investigated the feasibility, tolerance, and efficacy of $\beta$-all-trans retinoic acid (ATRA) and retinyl acetate gel delivered via a collagen sponge/cap insert in patients with CIN 1–3 (12–15). The results of these early trials raised considerable enthusiasm about the potential potent chemopreventive effects of retinoids in patients with cervical dysplasia. Recent trials have included a placebo group in their design to allow for more accurate ascertainment of the true effect of retinoids on the effect on histological regression. In 1994, Meyskens et al. (16) reported the results of a randomized Phase II trial of ATRA delivered via a collagen sponge and cervical cap to 301 patients with CIN 2/3. The complete histological regression rate was 47% in patients with CIN 2 treated with ATRA compared with 27% in those patients treated with placebo ($P < 0.041$). No differences were noted between the two treatment arms in the patients with CIN 3 (25% ATRA versus 31% placebo). Follen et al. (17) reported recently the results of a randomized trial of 4-HPR administered orally in patients with high-grade cervical dysplasia. Although no significant toxicity was noted, patients treated with 4-HPR had lower rates of regression than placebo-treated patients. Specifically, there was a 25% response rate at 6 months in 20 evaluable patients in the 4-HPR arm and 44% response rate in the 16 evaluable patients in the placebo arm ($P = NS$). At 12 months, there was a 14% response rate in 14 evaluable patients in the 4-HPR arm and 50% response rate in the 16 evaluable patients in the placebo arm ($P = 0.04$). These placebo-controlled trials of retinoid-treated patients with CIN 2/3 mirrored in part the results of this study using the pan-retinoid receptor agonist...
aliiretinoin with respect to histological regression. In our study, no significant difference in histological regression was noted in aliiretinoin-treated CIN 2/3 patients when compared with the placebo-treated patients.

We recognize that this current study has several limitations. At the time this trial was designed, there was little information regarding the natural regression of CIN 2/3 over the relatively short period of 3 months. Most papers on this subject have evaluated regression rates over an extended period of time (at least 6–12 months) and have included patients with CIN 1, which have higher rates of spontaneous regression (18, 19). The aforementioned trial by Meyskens et al. (16) was the only published placebo-controlled chemoprevention trial in CIN 2/3 patients at the time of design of the current study; the trial by Meyskens et al. (16) reported an ~30% regression rate in placebo-treated CIN 2/3 patients after 15 months of therapy. Thus, for the current study, a relatively small rate of regression (5%) in the placebo arm was anticipated given the short 12-week interval of treatment. The higher than anticipated regression rate (32%) in the placebo treated group realized in this study over 12 weeks may have been the result of removal of a significant part of the cervical lesion or the inflammatory response associated with tissue healing after biopsy of the cervix. Underestimating the regression rate in the placebo group in this study contributed to an underpowered study incapable of detecting a small but potentially significant benefit of aliiretinoin as a chemopreventive agent in cervical dysplasia.

As pointed out in a recent commentary by Follen et al. (20), this potential flaw in the statistical design has been recognized to be a common phenomenon in many chemoprevention trials, such as this one, that may make interpreting the effect of a specific chemoprevention agent on histological regression in cervical dysplasia difficult to accurately ascertain. Nevertheless, this study provides important contemporary information regarding regression rates of cervical dysplasia over a relatively short period of time in biopsied CIN 2/3 patients. The high regression rate in placebo-treated patients experienced in this trial and others would mandate accrual of a larger CIN 2/3 patient population to achieve adequate power in future trials investigating the utility of a specific chemopreventive agent in this disease context. However, the sample size for such trials could be tempered by designing studies that would be adequately powered to detect a 30–50% increase in histological regression in CIN 2/3 patients treated with a chemopreventive agent when compared with placebo-treated controls, a magnitude of effect as suggested by Follen et al. (20) that would be of clinical significance over current approaches to treating patients with cervical dysplasia. In addition, this study was limited by imbalance in CIN subpopulations within the various treatment groups and by potentially biased assessment of compliance. Employment of a stratified randomization procedure in future trials would allow for improved CIN subpopulation balance and for more accurate evaluation of chemoprevention effect in these distinct populations. Assessment of aliiretinoin serum levels in all of the patients would have provided more quantitative information to assess compliance with assigned treatment regimen.

This study was also configured to evaluate the effect of aliiretinoin on the modulation of surrogate end point biomarkers (19, 21, 22). These studies are currently in progress, and may provide important insights on the efficacy of aliiretinoin at these dosages in modulating the molecular and cellular processes involved with neoplastic transformation in the cervix. The results of these studies may also provide additional insights as to whether statistical design concerns noted in the evaluation of the histological effect of a chemopreventive agent in the cervix will also apply to the evaluation of surrogate end point biomarkers. Of note, the majority of cervical dysplasia chemoprevention trials including this one have failed to assess the effect of a chemopreventive agent on cervicovaginal HPV infection, an important biomarker in this disease context. Future trials should address this limitation by assessing HPV status over time in all of the treatment groups.

What insights regarding the role of retinoids as chemopreventive agents for patients with CIN can we derive from the results of this study and that of other retinoid-based chemoprevention trials. It would appear that the studies to date would suggest that topical retinoids have been more effective than what was experienced in the current trials investigating p.o. administered 4-HPR and aliiretinoin. However, the magnitude of efficacy noted with retinoid agents applied topically to the cervix appears to be modest and less than what would be clinically important given that high-grade cervical dysplasia is rather easily and efficiently treated in the outpatient setting with a loop procedure. Additionally, the ease of administration and patient compliance are issues associated with either physician- or patient-directed topical cervical interventions. In addition, the chemopreventive agent used in the context of CIN must have minimal side effects. That has not proven to be the case, particularly with p.o.-administered retinoids. In our study, headaches proved to be a clinically significant problem, particularly in the high-dose aliiretinoin group. Secondly, other laboratory side effects such as anemia, hypertriglyceridemia, and diminished HDLs would also preclude long-term use of this agent. These toxicities would likely prohibit significant escalation of the dose or duration of aliiretinoin to achieve the desired effect on histological regression. The potential toxicities associated with 4-HPR also diminish its potential use as a chemopreventive agent in this disease context, particularly on a chronic basis.

Chemoprevention is but one of many strategies to investigate in an effort to reduce the risk of invasive cervical cancer. How much retinoid-based chemoprevention strategies will add to cervical cancer risk reduction over identifying novel vaccine approaches, improving access to screening in underserved pop-

<table>
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<tr>
<th>Author No. patients</th>
<th>Agent/dose</th>
<th>Placebo/dose</th>
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<tr>
<td>Meyskins (12) 18</td>
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<td>None</td>
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<td>None</td>
<td>CIN 1/2</td>
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<td>CIN 1–3</td>
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<td>Inert vehicle</td>
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<td>Yes</td>
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ulations, and developing new screening paradigms remains to be elucidated.

Acknowledgments

We thank Dr. Philip Roland for assistance in initiating this trial and previous pilot cervical dysplasia chemoprevention studies at the University of Alabama at Birmingham. Thinprep vials and cervical brushes were generously provided by Cytyc Corporation.

References

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