A Phase I Study of *myo*-Inositol for Lung Cancer Chemoprevention

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Abstract

Introduction: **A phase I, open-label, multiple dose, dose-escalation clinical study was conducted to assess the safety, tolerability, maximum tolerated dose, and potential chemopreventive effect of *myo*-inositol in smokers with bronchial dysplasia.**

Materials and Methods: **Smokers between 40 and 74 years of age with ≥ 30 pack-years of smoking history and one or more sites of bronchial dysplasia were enrolled. A dose escalation study ranging from 12 to 30 g/d of *myo*-inositol for a month was first conducted in 16 subjects to determine the maximum tolerated dose. Ten new subjects were then enrolled to take the maximum tolerated dose for 3 months. The potential chemopreventive effect of *myo*-inositol was estimated by repeat autofluorescence bronchoscopy and biopsy.**

Results: **The maximum tolerated dose was found to be 18 g/d. Side effects, when present, were mild and mainly gastrointestinal in nature. Using the regression rate of the placebo subjects from a recently completed clinical trial with the same inclusion/exclusion criteria as a comparison, a significant increase in the rate of regression of preexisting dysplastic lesions was observed (91% versus 48%; $P = 0.014$). A statistically significant reduction in the systolic and diastolic blood pressures by an average of 10 mm Hg was observed after taking 18 g/d of *myo*-inositol for a month or more.**

Conclusion: ***myo*-Inositol in a daily dose of 18 g p.o. for 3 months is safe and well tolerated. The potential chemopreventive effect as well as other health benefits such as reduction in blood pressure should be investigated further.** (Cancer Epidemiol Biomarkers Prev 2006;15(8):1526–31)

Introduction

myo-Inositol (also known as inositol, hexahydroxycyclohexane, or *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol) is an isomer of glucose that is a precursor in the phosphatidylinositol cycle. It is a source of several second messengers including diacylgycerol, which regulates some members of the protein kinase C family, inositol-1,4,5-triphosphate, which modifies intracellular calcium levels, and phosphatidylinositol-3,4,5-biphosphate, which is involved in signal transduction. It is a component of cell membranes and is an essential nutrient required by human cells for growth and survival in culture.

The primary naturally occurring source of *myo*-inositol is inositol hexaphosphate, which is hydrolyzed in the gastrointestinal tract to free *myo*-inositol by the enzyme phytase. Inositol hexaphosphate is found in a wide variety of foods such as whole grains, seeds, and fruits. Free inositol has extremely low toxicity. The oral mouse LD_{50} is 10 g/kg (1). In humans, *myo*-inositol has been investigated in the treatment of psychiatric disorders such as depression, obsessive-compulsive disorder, and panic attacks (2-7), as well as in the treatment of diabetic neuropathy (8, 9). No serious adverse effects were observed in doses up to 20 g/d p.o. for up to 6 weeks. However, the safety and tolerability of large doses of *myo*-inositol administered for more than 2 to 6 weeks have not been studied in humans.

Dietary inositol has been shown to inhibit lung tumorigenesis in female A/J mice exposed to the carcinogen benzo(*a*)-pyrene or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone in a number of studies (10-17). With doses as low as 0.3% *myo*-inositol added to the diet, *myo*-inositol inhibited pulmonary tumor formation by 53% when given continuously starting 1 week before benzo(*a*)pyrene administration (11). *myo*-Inositol was also effective in the post-initiation phase (13) and when given for short periods of time before, during, and immediately post carcinogen exposure (16). The combination of *myo*-inositol with inhaled budesonide was significantly more effective than either agent alone (11). There is little information on the mechanism or mechanisms by which *myo*-inositol produces chemoprevention in the human respiratory tract. Some studies have been carried out in human breast cancer cells, small airway cells, and endothelial cells *in vitro* (18-22). To further our understanding of the chemopreventive effects of *myo*-inositol in the human, we did a phase I, open-label, multiple dose, dose-escalation clinical trial to assess safety, tolerability, and the maximum tolerated dose of *myo*-inositol in high-risk current and former smokers with bronchial dysplasia. Preliminary assessment of efficacy was obtained through serial biopsies of bronchial mucosa during autofluorescence bronchoscopy.

Materials and Methods

Study Population. Current and former smokers between 40 and 74 years of age, ≥30 pack-year smoking history, and one or more sites of bronchial dysplasia on autofluorescence bronchoscopy were invited to take part in this study. The participants in the dose escalation part of the study were individuals with persistent dysplasia despite treatment with inhaled budesonide during participation in a previously reported National Cancer Institute–funded study (23). All participants had stopped taking budesonide for a minimum of 6 months (median, 21 months; range, 7-31 months). After establishing the maximum tolerated dose (described below),

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10 new subjects with bronchial dysplasia who had not previously been treated with inhaled corticosteroids were recruited for the final 3-month study. Pretreatment bronchoscopy was done within 3 weeks of initiation of treatment. Individuals were excluded if they had a history of schizophrenia, bipolar disorder, or diabetes.

The Clinical Investigations Committees of the British Columbia Cancer Agency and the University of British Columbia approved this study. Written informed consent was obtained from all participants.

Study Procedures. Following a history and physical examination, informed consent about the study was obtained. Pretreatment blood tests consisting of fasting blood glucose, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, electrolytes, blood urea nitrogen, creatinine, calcium, phosphate, thyroid stimulating hormone, cholesterol, triglyceride, and complete blood count were obtained. If the test results were within normal limits, *myo*-inositol was started according to the dose escalation schema described in detail below. All participants were allowed to dose escalate once. A history and physical examination, as well as all the blood tests, were repeated monthly while on treatment. A telephone interview was done 1 week after the first dose or after the first dose escalation. A follow-up interview was conducted 1 month after completion of treatment. Toxicity was monitored according to the National Cancer Institute common toxicity criteria (version 2.0).[4] Participants with grade $\geq$2 toxicity were interviewed and their blood tests repeated weekly until the symptoms had resolved or the blood test results had returned to normal. Autofluorescence bronchoscopy and bronchial biopsy of areas with dysplasia before treatment and new areas suspicious for dysplasia were done at the end of the 2- or 3-month intervention. The potential efficacy of *myo*-inositol was estimated by repeat autofluorescence bronchoscopy (23) and biopsy of preexisting dysplastic lesions and/or any new lesions appearing at the end of the treatment.

Dosing Period and Dose Escalation Procedure. Based on the order of entry to the study, the participants received, in a dose escalation schema, one of four dose levels (12, 18, 24, or 30 g) of *myo*-inositol mixed with juice or water divided into two doses daily (e.g., lowest dose, 6 g bid). The *myo*-inositol was a gift from Tsuno Food Industries Co., Ltd. (Wakayama, Japan). Chemical analysis by the company showed that it was 99.5% pure with heavy metals <10 ppm and no microbial contamination. Four to ten subjects were enrolled into one of four treatment groups (12, 18, 24, or 30 g of *myo*-inositol p.o. per day in two divided doses) starting with the lowest dose for 1 month. Subjects without grade $\geq$2 toxicity (National Cancer Institute Common Toxicity Criteria) were allowed to dose escalate once for an additional month. Therefore, at least four and as many as six new participants were enrolled at each dose level. In addition, up to six participants who had finished 1 month of treatment at the previous dose level were escalated to the next higher dose level. New participants were recruited to the next higher dose level only if $\leq$30% of the participants had grade $\geq$2 toxicity that was possibly or probably related to *myo*-inositol. If 4 of 10 participants had grade $\geq$2 toxicity, dose escalation was discontinued and that dose was defined as having exceeded the maximum tolerated dose. The dose below the nontolerated dose was defined as the maximum tolerated dose. Ten new participants were then enrolled at the maximum tolerated dose for 3 months.

[4] http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf.

Data Analysis. All participants who had taken one or more doses of the intended course of treatment were included in the analyses. Descriptive statistics were used to summarize subject characteristics and pathologic evaluations of the bronchial biopsy specimens. Exploratory analysis of potential efficacy was made by comparing the bronchial biopsies obtained before and after treatment with *myo*-inositol with those from a placebo group of a phase II, double-blind, randomized, placebo-controlled trial of inhaled budesonide with similar enrollment criteria (23). Pearson's χ^2 test with continuity correction was used to compare response rates (progression and regression) in the two arms. All P values were two sided. Two-sided $P < 0.05$ was considered statistically significant.

The primary end point of the study was safety. All subjects who received at least one dose of study medication were included in the analysis of safety. The incidence of adverse events, toxicities, as well as laboratory abnormalities, was summarized by treatment group. The secondary end point was preliminary assessment of the chemopreventive efficacy of *myo*-inositol by a change in the histopathology grade of the bronchial biopsy samples before and after treatment. The bronchial biopsies were systematically reviewed by an experienced lung pathologist (J.C.L.). The pathologist was blinded to the treatment (i.e., pretreatment or posttreatment biopsy). All biopsy samples were classified into one of the following seven groups according to WHO criteria (24): normal (as represented by pseudostratified ciliated columnar epithelium); basal cell hyperplasia (as represented by an increase in the number and stratification of normal-appearing basal cells still covered with normal ciliated or mucin-secreting cells); metaplasia (as represented by a stratified epithelium and cytoplasmic changes consistent with squamoid differentiation); dysplasia (mild, moderate, or severe); and carcinoma *in situ*. Because individual biopsies frequently contained more than one histologic cell type, the diagnosis was based on the most advanced histology present. For the lesion-specific analysis, complete response was defined as the regression of a dysplastic lesion to one classified as being either hyperplastic or normal. Progressive disease was defined as appearance of lesions that were classified as mild dysplasia or worse, irrespective of whether the site was biopsied at baseline, or worsening of the dysplastic lesion present at baseline by two or more grades (e.g., mild dysplasia to severe dysplasia or worse). Dysplastic lesions that were not classified as complete response or progressive disease were referred to as stable disease. A subject-specific analysis was also done to control for correlation from multiple lesions in the same individual. Complete response was defined as follows: complete response referred to regression of all dysplastic lesions found at baseline to lesions that were no worse than hyperplasia, as defined by the site by site analysis at follow-up evaluation, and the appearance of no new dysplastic lesions that were mild dysplasia or worse. Progressive disease was defined as progression of one or more sites by two or more grades as defined for the lesion-specific analysis above, or the appearance of new dysplastic lesions that were mild dysplasia or worse at follow-up evaluation. Partial response was defined as regression of some but not all of the dysplastic lesions with the appearance of no new lesions that were mild dysplasia or worse. Stable disease referred to subjects who did not have a complete response, partial response, or progressive disease. These response criteria have previously been described (23).

Results

Clinical Characteristics. A total of 26 individuals were enrolled into the study. The characteristics of these participants are shown in Table 1. Fifty-eight percent of them were

Table 1. Characteristics of study participants

Characteristics	Ex-smokers	Current smokers	Total
N	11	15	26
Age (y)			
Mean ± SD (range)	63 ± 8 (48-72)	61 ± 7 (48-73)	62 ± 8 (48-73)
Sex			
Male	10	14	24
Female	1	1	2
Smoking history, pack-years			
Mean ± SD (range)	50 ± 25 (30-108)	56 ± 19 (30-90)	53 ± 22 (30-108)
Years stopped	9 ± 7 (2-21)		
Highest dysplasia grade in baseline biopsy			
Mild	10	13	23
Moderate	1	1	2
Severe	0	1	1
≥2 sites of dysplasia (*n*)	4	7	11

current smokers and 42% were former smokers. All had smoked heavily with an average of 53 pack-years. Forty-two percent of the participants had two or more sites of bronchial dysplasia.

The number of individuals enrolled into each of the four dose levels is shown in Table 2. One of the six participants at the 12 g/d dose level did not dose escalate because of grade 2 diarrhea. Two participants in the 18 g/d dose group did not dose escalate because of grade 2 or 3 diarrhea. Four participants in the 24 g/d dose group did not dose escalate—two because of grade 2 diarrhea and two because of multiple grade 2 gastrointestinal symptoms. The maximum tolerated dose of *myo*-inositol was found to be 18 g/d. Two participants were able to dose escalate to the final 30 g/d dose from 24 g/d dose. Both had mild grade 1 gastrointestinal symptoms only. Ten new participants were enrolled to the 18 g maximum tolerated dose level for 3 months. All except one of these participants were able to complete the 3-month study. The one participant who dropped out had a family history of colon cancer and was taken off the study during month 3 because of admission to hospital for removal of a villous adenoma.

Compliance. Compliance with the *myo*-inositol was excellent. As a group, the participants took 90 ± 15% of the prescribed dose. The 10 participants who were on the 18 g/d dose for 3 months took 96 ± 6% of the prescribed dose.

Adverse Events. The frequencies and severity of adverse symptoms possibly, probably, or likely to be related to intake of *myo*-inositol are shown in Table 3. Adverse events, aside from gastrointestinal symptoms, were infrequent and mild. The most frequently reported symptoms were flatulence, loose stool, or diarrhea. In general, participants who had been taking a lower dose were able to tolerate the higher dose better than those taking the higher dose for the first time. For the 10 participants in the 18 g/d dose 3-month study, mild gastrointestinal symptoms were experienced for the first month only.

Laboratory monitoring tests showed grade 1 elevation of fasting blood sugar in one of the six participants taking the 12 g/d dose. However, the blood glucose returned to normal in the second month while taking a higher dose of *myo*-inositol (18 g/d). One of the two participants on the 30 g/d dose also had transient elevation of the fasting blood glucose. Mild hypophosphatemia was observed in 5 of the 19 participants on the 18 g dose and 1 of the 6 subjects on the 12 g/d dose. A grade 2 decrease in lymphocytes was observed during month 2 of one individual on the 18 g dose level but resolved spontaneously at month 3.

There was a slight increase in the hemoglobin after taking 18 g/d of *myo*-inositol for 1 month (baseline: 143 ± 6 g/L; month 1: 147 + 7; month 2: 150 ± 7 g/L; month 3: 148 ± 4 g/L). The increase was statistically significant in months 2 and 3 ($P = 0.02$ and 0.021, respectively, paired t test). The total and differential white counts, as well as platelet counts, were similar at all time points and dose levels.

Effect of *myo*-Inositol on Body Weight and Blood Pressure. The body weight did not change significantly after taking *myo*-inositol 18 g/d for 3 months (Table 4). However, there was a significant reduction of the diastolic blood pressure after 1 month (89 ± 9 versus 76 ± 13 mm Hg; $P = 0.021$). The systolic blood pressure also decreased significantly at months 2 and 3 (127 ± 12 and 134 ± 19 mm Hg versus 148 ± 16 mm Hg at baseline; $P = 0.001$ and $P = 0.01$, respectively). Seven of the 10 participants had preexisting hypertension and one received antihypertensive treatment before enrollment into the study. There was no change in the dose of the antihypertensive drug in this participant. As a group, five of the nine participants who completed the 3-month treatment had >10 mm Hg decrease in their systolic blood pressure and six of the participants had >10 mm Hg decrease in their diastolic blood pressure.

Potential Chemopreventive Effects of *myo*-Inositol. The effects of *myo*-inositol on regression of existing dysplastic lesions and prevention of development of new lesions after taking *myo*-inositol 18 g/d for 3 months are shown in Table 5. Nine of the 10 participants were former smokers whereas one participant smoked fewer than 10 cigarettes per day intermittently during the study. Using the progression and regression rates of the placebo subjects from a recently completed chemoprevention trial with the same inclusion and

Table 2. Number of participants in dose escalation study

Level I: 12 g (6 g bid)	Level II: 18 g (12 g a.m. and 6 g p.m.)	Level III: 24 g (12 g bid)	Level IV: 30 g (18 g a.m. and 12 g p.m.)
6	5 from level I,*† 4 new	2 from level II,‡ 6 new	2 from level III§

*Each subject could dose escalate at the end of 1 month once if grade <2 toxicity.
†One subject did not dose escalate from level I because of grade 2 diarrhea.
‡Two subjects did not dose escalate from level II because of grade 2 or 3 diarrhea respectively.
§Four subjects did not dose escalate from Level III—two because of grade 2 diarrhea and two with multiple grade 2 gastrointestinal symptoms.

Table 3. Adverse events

Toxicity	*myo*-Inositol dose														
	12 g, $N = 6$			18 g, $N = 9$			24 g, $N = 8$			30 g, $N = 2$			18 g 3 months, $N = 10$		
Grade	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Constitutional															
Decreased appetite	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—
Mood fluctuation	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Body aches	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Thirst	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Endocrine															
Decreased body temperature	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
Gastrointestine															
Bloating	2	—	—	—	—	—	1	—	—	—	—	—	1	—	—
Constipation	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
Diarrhea	—	1	—	—	1	1	—	1	—	—	—	—	3	—	—
Flatulence	6	—	—	3	—	—	2	—	—	1	—	—	6	—	—
↑Bowel movement	—	—	—	2	—	—	—	2	—	—	—	—	2	—	—
Urgency	1	—	—	2	—	—	—	3	—	1	—	—	2	—	—
Loose stool	4	—	—	3	—	—	2	2	—	—	—	—	2	—	—
Nausea	1	—	—	1	—	—	1	—	—	—	—	—	—	—	—
↑Peristalsis	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
Head and neck															
Congestion	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
Headache	—	—	—	—	—	—	—	—	—	—	—	—	2	—	—
Sinus drainage	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Light headed	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Musculoskeletal															
Arthritis	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
Neurologic															
Depression	1	—	—	1	—	—	—	—	—	—	—	—	—	—	—
Vivid dreams	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Pain															
Migraine	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Abdominal	—	—	—	1	—	—	1	—	—	1	—	—	—	—	—
Anus	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pulmonary															
Cough	—	—	—	1	—	—	—	—	—	—	—	—	1	—	—
Renal:															
Increase urination	1	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Mouth															
Bad taste	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Dermatology															
Itchy skin	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
Blood															
Lymphopenia	1	—	—	—	—	—	—	—	—	—	—	—	—	1	—
↓Phosphate*	1	—	—	1	—	—	—	—	—	—	—	—	4	—	—
↑Potassium	1	—	—	2	—	—	2	—	—	—	—	—	—	—	—
↑Alkaline phosphatase	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Elevated fasting															
Blood glucose	—	—	—	1	—	—	—	—	—	1	—	—	—	—	—
Hyponatremia	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—
Hypercholesterol	—	—	—	—	—	—	—	—	—	1	—	—	1	—	—
↑Triglyceride	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—

*Defined as <LLN 0.53 mmol/L.

exclusion criteria (18), there was a statistical increase in the regression rate in the lesion specific analysis (91% versus 48%; $P = 0.014$). There was also a borderline significant increase in the complete response rate in the person-specific analysis (67% versus 28%; $P = 0.06$) although the number of subjects was very small. There was a decrease in the progression rate in both the lesion-specific analysis (4.1% versus 9.2%; $P = 0.35$; Table 5) and person-specific analysis (22% versus 51%; $P = 0.22$) but this difference did not reach statistical significance. A similar trend in the increase in regression rates and reduction in progression rates was also observed among subjects in the dose escalation portion of this study who took 18 g or higher doses of *myo*-inositol for 1 to 2 months (data not shown).

Table 4. Changes in body weight and blood pressure with 18 g/d of *myo*-inositol for 3 months

	Weight (lbs)	Systolic (mm Hg)	Diastolic (mm Hg)
Baseline, $N = 10$	203 ± 33* (156-260)	148 ± 16 (120-180)	89 ± 9 (70-100)
Month 1, $N = 9$	202 ± 37 (160-263)	141 ± 18 (115-160), $P = 0.142$	76 ± 13 (60-100), $P = 0.021$
Month 2, $N = 10$	203 ± 32 (160-260)	127 ± 12 (100-145), $P = 0.001$	74 ± 14 (40-90), $P = 0.029$
Month 3, $N = 9$	208 ± 32 (162-260)	134 ± 19 (110-157), $P = 0.015$	75 ± 6 (66-89), $P = 0.001$

*Mean ± SD; numbers in parentheses represent the range.

Table 5. Changes in pathologic grades of bronchial biopsy samples at baseline and after 3 months of *myo*-inositol (18 g): Lesion-specific analysis

Pathologic grades of bronchial biopsies at baseline	Status after 3 months of treatment			
	N	Stable	Regression*	Progression†
Placebo group (from ref. 18)				
Normal/hyperplasia/metaplasia	256	219	0	37
Mild dysplasia	134	72	62	0
Moderate/severe dysplasia	13	5	8	0
myo-Inositol group				
Normal/hyperplasia/metaplasia	38	36	0	2
Mild dysplasia	10	1	9	0
Moderate/severe dysplasia	1	0	1	0

*Biopsy samples that represent a complete response during the intervention period. Only sites of dysplasia could regress to normal/hyperplasia. Complete response was 91% (10 of 11) and 47.6% (70 of 147) in the *myo*-inositol and placebo groups, respectively ($P = 0.014$, two-sample test for equality of proportions with continuity correction).

†Sites of any grade at baseline could progress. Progress disease includes appearance of new dysplastic lesions. It was 4.1% (2 of 49) and 9.2% (37 of 403) in the *myo*-inositol and placebo groups, respectively ($P = 0.35$, two-sample test for equality of proportions with continuity correction).

Discussion

In humans, *myo*-inositol has been studied in the treatment of psychiatric disorders such as depression, obsessive-compulsive disorder, and panic attacks (2-7), as well as diabetic neuropathy (8, 9). No serious adverse effects were observed in doses up to 20 g/d p.o. for 2 to 6 weeks. Minor symptoms such as nausea, abdominal pain, flatulence, or soft stools were reported in only a small proportion of the subjects treated (3, 7). The results of blood tests, when reported, usually stated that no hematologic, renal, or liver function abnormality was observed, although the actual laboratory values were not shown. In the only study where abnormal laboratory results were reported (3), 2 of the 13 patients who received *myo*-inositol 12 g/d for 4 weeks for treatment of depression showed a mild increase in the fasting blood glucose. In one subject, the blood glucose returned to normal despite continuing to take *myo*-inositol after the clinical trial. The second patient showed the same mild increase several weeks after discontinuation of *myo*-inositol.

Our study confirms that *myo*-inositol, in a dose of 18 g/d for up to 3 months, was well tolerated. Adverse events, when present, were mainly gastrointestinal in nature and mild. Transient mild elevation of the fasting blood glucose was observed in 2 of the 26 subjects—one while taking 12 g/d of *myo*-inositol that returned to normal despite escalating the dose to 18 g/d in the second month of treatment. The other subject had mild elevation of the blood glucose after increasing the dose from 24 to 30 g/d. Mild decrease in serum phosphate was observed in 6 (23%) of the subjects not associated with any clinical symptoms. The clinical significance of this decrease is not known.

In this study, we observed that subjects who were started on a lower dose were more likely able to tolerate a higher dose compared with those who took the higher doses for the first time. In the 10 subjects who were on the 18 g/d dose for 3 months, the mild gastrointestinal symptoms experienced during the first month resolved in the second month. Two subjects who were started on the 24 g dose were able to tolerate the 30 g dose for 3 months with grade 1 toxicity only. These results suggest that, if *myo*-inositol were administered for therapeutic purposes, it should be given at a lower dose such as 12 g/d first before increasing to a higher dose such as 18 g/d.

An unexpected but potentially important finding was a significant decrease in the blood pressure after taking *myo*-inositol for a month or more. There was also a statistically significant, although probably clinically insignificant, increase in the hemoglobin after taking 18 g of *myo*-inositol for more than 4 weeks. It is beyond the scope of our current study to determine if *myo*-inositol could be useful for treatment of anemia of chronic disease or for prevention of anemia associated with cytotoxic chemotherapy. The potential antihypertensive effect we observed in this study has more clinical ramifications and should be investigated in future studies.

Although the goal of this study was to examine the tolerability of 3 months of treatment with *myo*-inositol and the study was not powered to detect efficacy, significant regression of individual dysplastic lesions was identified. These data, although intriguing, are very preliminary because only a small number of participants were treated in this study and the comparison group, consisting of historical controls from a prior trial with similar eligibility criteria, had been studied up to several years prior. Nevertheless, we have previously shown that the rates of regression of dysplastic lesions in two different chemoprevention trials conducted years apart were remarkably similar at 48% and 41%, respectively (23, 25). Taken together with preclinical studies showing *myo*-inositol to be an effective agent in lung cancer prevention when used alone or even more effective when combined with other agents, such as glucocorticoids or *N*-acetyl-*S*-(*N*-2-phenethylthiocarbamoyl)-L-cysteine (10, 11, 17), our exploratory study suggests that *myo*-inositol may be effective in regression of preexisting bronchial dysplasia when given at a daily dose of 18 g or higher. The low toxicity and excellent compliance with this regimen argue for further investigation of its chemopreventive effect in smokers at high risk for lung cancer in phase II randomized placebo-controlled trials.

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