Selenomethionine and Celecoxib Are Ineffective as Chemoprevention for Esophageal Squamous Cell Cancer

Limburg PJ, Wei W, Ahnen DJ, et al. Randomized, placebo-controlled, esophageal squamous cell cancer chemoprevention trial of selenomethionine and celecoxib. Gastroenterology 2005;129:863–73.

Study Overview

Objective. To determine the effects of selenomethionine (a synthetic form of organic selenium) and celecoxib among individuals at high risk for esophageal squamous cell carcinoma (ESCC).

Design. Randomized, double-blind, placebo-controlled trial with a 2 × 2 factorial design.

Setting and participants. Subjects were recruited from among a population of residents of Linxian, China, aged 26 to 73 years, who underwent esophagogastroduodenoscopy screening with mucosal iodine staining. Individuals with 1 or more grossly visible lesions and biopsy-proven mild or moderate dysplasia were eligible to participate. Patients were excluded if they had a history of cancer, symptoms suggestive of an upper gastrointestinal tract malignancy, peptic ulcer disease, or any contraindication to selenomethionine or celecoxib therapy.

Intervention. Participants were randomized using a variable block approach (1:1:1:1 ratio) to 1 of 4 groups: active selenomethionine and active celecoxib, active selenomethionine and placebo celecoxib, placebo selenomethionine and active celecoxib, or placebo selenomethionine and placebo celecoxib. Active selenomethionine (200 μg) was given once daily, and active celecoxib (200 mg) was administered twice daily. The trial duration was 10 months.

Main outcome measures. The primary outcome was the change in histologic grade of squamous dysplasia between baseline and the end of the trial. Histologic grades included no evidence of dysplasia, mild dysplasia, moderate dysplasia, severe dysplasia, and invasive cancer. For patients with mild dysplasia at baseline, progression was defined as moderate dysplasia, severe dysplasia, or invasive cancer, and regression was defined as no evidence of dysplasia at the end-of-trial evaluation. For patients with moderate dysplasia at baseline, progression was defined as severe dysplasia or invasive cancer, and regression was defined as no evidence of dysplasia or mild dysplasia at the end-of-trial evaluation. Patients with no histologic change were categorized as having stable disease. Squamous dysplasia was chosen as the surrogate end marker because it strongly predicts ESCC risk and can be readily visualized on mucosal iodine staining. All biopsies were independently reviewed by 2 blinded gastrointestinal pathologists.

Main results. Of 549 individuals evaluated at baseline, 360 were randomized. After randomization, 93 patients were excluded based on their biopsy samples, and 29 did not complete the end-of-trial evaluation, resulting in 238 patients in the final cohort. Baseline characteristics were similar between the groups. For all patients, active selenomethionine resulted in a nonsignificant increased regression and decreased progression when compared with placebo selenomethionine (43% versus 32% and 14% versus 19%, respectively). No changes in regression or progression were seen in the celecoxib group, and no interaction was found between selenomethionine and celecoxib. In unplanned stratified analyses, selenomethionine had a statistically significant favorable effect in patients with baseline mild squamous dysplasia, resulting in increased lesion regression (39% versus 21%) and decreased progression (19% versus 36%) compared with placebo (P = 0.02). No statistically significant effect of selenomethionine was seen in the moderate dysplasia subgroup.

Conclusion. Neither selenomethionine nor celecoxib significantly altered esophageal squamous dysplasia histology after 10 months in high-risk patients. For patients with mild dysplasia at baseline, selenomethionine appeared to have a protective effect.

Commentary

ESCC is a common cause of cancer death worldwide and has a 5-year survival rate of less than 10% [1]. In the United States, it is estimated that almost 90% of ESCC cases are related to modifiable lifestyle risk factors, such as smoking, alcohol use, and diets low in fruit and vegetables [2]. Although ESCC is less common in Western nations as compared with the rest of the world, the poor prognosis and lack of effective

treatments have promoted the search for chemopreventive agents [3]. Observational studies in China have suggested that selenium deficiency may be a risk factor for ESCC and that selenium supplementation may reduce this risk [4]. Along with selenium, cyclooxygenase-2 inhibitors might also be protective, but data from controlled trials are lacking.

Limburg et al's trial was designed to determine if selenium (given as selenomethionine) or celecoxib (alone or in combination with selenium) could be used as chemoprevention for ESCC. Unfortunately, the results were not impressive; neither agent seems to be chemoprotective. However, several limitations of the trial could have contributed to its null finding. First, the duration of follow-up was only 10 months, and it is unclear if beneficial effects would be seen with a longer duration of use. Second, the trial was small and had limited power. Finally, the investigators used a surrogate endpoint (ie, esophageal squamous dysplasia); however, this seems to be justifiable substitution. While a favorable effect was found in patients with mild dysplasia, this was not a planned analysis and would require further evaluation.

Applications for Clinical Practice

For patients with esophageal squamous dysplasia, neither selenomethionine nor celecoxib appears to be chemopreventive for ESCC. However, selenomethionine may be helpful in patients with mild dysplasia. Providers should continue to promote lifestyle changes to patients at risk for ESCC.

–Review by Harvey J. Murff, MD, MPH

References

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