Effects of a Genistein-Rich Extract on the Recurrence Rate of Superficial Bladder Cancer

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A. Introduction

Bladder cancer is the most common malignancy affecting the urinary system. In the United States, approximately 60,000 individuals develop this disease and 13,000 die from it each year. Epidemiologists have noted that globally, the incidence of bladder cancer varies approximately 10-fold, with Western Europe and North America having the highest and Eastern Europe and Asian countries having the lowest rates (1). This is true despite the fact that smoking--the single most important risk factor for the development of urothelial tumors--is more prevalent in Asia (2). Interests in dietary variations that may account for the differences in cancer rates have focused on the high soy consumption among Asians.

We know that soybean products contain large amounts of the isoflavones (3). These compounds have molecular weights and structures similar to those of steroids and are known to have estrogenic and antiestrogenic activities as well as growth-inhibitory activities that appear independent of estrogen receptors (4). Biochemical studies of isoflavone activity along with the observed correlation between soybean product intake and the urinary excretion of isoflavonoids suggest a possible role for isoflavones in treatment of bladder cancer.

Laboratory studies of isoflavones and bladder cancer support a role for isoflavone in bladder cancer therapy. Zhou et al examined the effect pure soy isoflavones (genistein, genistin, daidzein, and biochanin A) and soy phytochemical concentrate on the growth of murine and human bladder cell lines in vitro and in vivo (5). They showed the soy isoflavones exhibit a dose-dependent growth inhibition of the bladder cancer cell lines. In mice inoculated with murine bladder carcinoma cells that were fed a genistein or soy products enriched diet, they found decreased tumor size, reduced angiogenesis, increased apoptosis, and slightly reduced proliferation but no histopathological effects on the normal bladder mucosa. The anti-tumor activity of soy isoflavones was corroborated by the work of Su et al. They showed that genistein tends to cause a dose-dependent induction of G2-M cell cycle arrest and an inhibition of cdc2 kinase activity but, both daidzein and biochanin-A directly induced apoptosis without altering cell cycle distribution (6). In fact, an equal mixture of the three isoflavones was more effective in growth inhibition and apoptosis induction than any single compound. In mice with engrafted tumors, they observed a significant reduction of tumor size with administration of the isoflavones. Notably, all results were achieved using concentrations of isoflavones found in the range of human urine excretion. Other studies of isoflavones' growth inhibitory activity with regards to bladder cancer have identified the EGFR and Her2 Neu as possible biochemical targets (7, 8). Despite the provocative results of animal and cell studies, there are no clinical studies of soy isoflavones in bladder cancer patients to date.

One obstacle to the using of soybean products in cancer therapy not addressed by laboratory studies is that naturally occurring isoflavones are predominantly glycosylated and poorly absorbed. One solution to this problem is to ferment soy extract with mushroom mycelia. This process increases the bioavailability of isoflavone in soy because of hydrolysis by B-glucosidase produced by the organism. This product is currently sold in nutritional supplement stores in Japan, United States, and other countries and termed GCP (genistein combined polysaccharide; Amino Up Chemical Co., Sapporo, Japan) (9). GCP has already been used in a randomized clinical trial to evaluate its potential for lowering PSA levels in patients with prostate cancer (10). 62 men were enrolled in the study and consumed 5g of GCP daily for 6 months. There were no alterations in clinical chemistries and only three patients discontinued therapy due to diarrhea, which resolved on discontinuation of the supplement. Our laboratory has unpublished data on GCP and human bladder cancer cell lines that show a dose dependent growth

inhibitory effect on cell growth in vitro. Comparison of GCP with Genistein alone showed the GCP was more effective in inhibiting cell growth.

We will study the effect of GCP on decreasing the recurrence rate of superficial bladder cancer. Specifically, we are interested in patients with Ta Grade 1 disease. Patients presenting with Ta disease are followed up closely, usually with no additional therapy unless their cancer recurs more than two times in one year (11). If effective, GCP would could decrease a patient's likelihood of requiring more aggressive therapies like intravesical therapy or a cystectomy.

B. Hypothesis

We hypothesize that GCP will decrease the recurrence rate of superficial transitional cell carcinoma (TCC) in patients presenting with new superficial bladder cancer and in patients presenting with a recurrent superficial bladder cancer.

C. Methods

a. We will measure

1) Recurrence rate within the first year of a new diagnosis or following a recurrence. A patient who recurs two times in one year will be counted as two recurrences, three times counted as three recurrences etc. The total number of recurrences for each group will be divided by the number of subjects in that group to calculate a recurrence rate.
2) time to first recurrence. A patient recurring twice in one year will be counted as two recurrences.

b. Study Design

This will be a multi-institutional two arm, double-blinded randomized controlled trial of patients evaluating the efficacy of GCP in decreasing the recurrence rate of new and recurrent superficial bladder cancers. Patients presenting with a diagnosis of new superficial TCC or recurrent superficial TCC will be randomized to either a daily dose of 5g of GCP or placebo. Randomization will be stratified based on whether the patient is a new or recurrent bladder cancer case. Patients will receive a cystocopy, urine cytology, and intravenous pyelogram every 3 months for a total of 12 months to look for evidence of recurrent neoplasm. All incidences of recurrence must be based on histology.

c. Statistical Analysis

Recurrence rates of the control vs. experimental groups will be compared using logistical regression the new vs. recurrent as an additional factor besides the treatment. Cox proportional hazards ratios will also be calculated. The secondary outcome of time to recurrence will be analyzed using Kaplan-Meier method.

d. Sample Size

We will need approximately 628 patients per arm for a total of 1256 patients. This will provide an 80% power to detect an decrease of 33% in recurrence rate with a p=.05. The sample size was derived by estimating the recurrence rate of patients with new superficial bladder cancer as 15% and the re-recurrence rate of patients with prior superficial bladder cancer as 20% (12, 13). At Columbia-Presbyterian's Department of Urology, we expect to see in one year about 180 patients with new superficial bladder cancer and 120 patients with recurrent superficial bladder cancers. Thus, to meet our sample size we will need to run the study at four centers.

D. Subject Selection

The study will recruit from all eligible patients seen in urology clinics at Columbia-Presbyterian Hospital and three other academic hospitals in New York City or surrounding area. We will include patients presenting with new or a recurrent Ta Grade I tumor. Exclusion criteria include multiple tumors, tumors greater than 3cm in diameter, severe dysplasia or carcinoma in situ found on selected biopsies of

non-tumor bearing areas, positive cytology, or intravesical or surgical therapy. These characteristics are excluded because they are risk factors for recurrence.

E. References

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