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Soy Isoflavones in Conjunction With Radiation Therapy in Patients With Prostate Cancer

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Abstract

Soy isoflavones sensitize prostate cancer cells to radiation therapy by inhibiting cell survival pathways activated by radiation. At the same time, soy isoflavones have significant antioxidant and anti-inflammatory activity, which may help prevent the side effects of radiation. Therefore, we hypothesized that soy isoflavones could be useful when given in conjunction with curative radiation therapy in patients with localized prostate cancer. In addition to enhancing the efficacy of radiation therapy, soy isoflavones could prevent the adverse effects of radiation. We conducted a pilot study to investigate the effects of soy isoflavone supplementation on acute and subacute toxicity (6 mo) of external beam radiation therapy in patients with localized prostate cancer. Forty-two patients with prostate cancer were randomly assigned to receive 200 mg soy isoflavone (Group 1) or placebo (Group 2) daily for 6 mo beginning with the first day of radiation therapy, which was administered in 1.8 to 2.5 Gy fractions for a total of 73.8 to 77.5 Gy. Adverse effects of radiation therapy on bladder, bowel, and sexual function were assessed by a self-administered quality of life questionnaire at 3 and 6 mo. Only 26 and 27 patients returned completed questionnaires at 3 and 6 mo, respectively. At each time point, urinary, bowel, and sexual adverse

symptoms induced by radiation therapy were decreased in the soy isoflavone group compared to placebo group. At 3 mo, soy-treated patients had less urinary incontinence, less urgency, and better erectile function as compared to the placebo group. At 6 mo, the symptoms in soy-treated patients were further improved as compared to the placebo group. These patients had less dripping/leakage of urine (7.7% in Group 1 vs. 28.4% in Group 2), less rectal cramping/diarrhea (7.7% vs. 21.4%), and less pain with bowel movements (0% vs. 14.8%) than placebo-treated patients. There was also a higher overall ability to have erections (77% vs. 57.1%). The results suggest that soy isoflavones taken in conjunction with radiation therapy could reduce the urinary, intestinal, and sexual adverse effects in patients with prostate cancer.

INTRODUCTION

Prostate cancer is the most common cancer in men, with 192,280 new cases in 2009 (1). Although the incidence is high, the 5-yr overall survival rate is above 90%, in part due to successful treatment of localized disease with surgery or radiotherapy (1). Treatment options for localized prostate cancer include radiation therapy, radical prostatectomy, hormone therapy, or combinations of various treatments depending on the aggressiveness of the disease. External beam radiation with or without hormones is one of the commonly used treatment options for localized prostate cancer (2).

Men with early stage prostate cancer who receive external beam radiation therapy (EBRT) are treated to the entire prostate and the caudal portion of the seminal vesicles. In order to adequately treat the prostate, adjacent normal structures are, by necessity, also irradiated. The bladder neck (superior), penile bulb (inferior), and the anterior rectal wall (posterior) all receive significant doses of radiation (3). Thus, the adverse effects of radiation are seen on the bladder, rectum, and erectile tissues. Most patients experience mild adverse effects, but 5–10% of patients experience significant urinary and intestinal toxicity (4). However, in clinical trials, underreporting of side effects often occurs, especially of lower grades; therefore, the extent of true toxicity may be much higher than reported (5). Because even low-grade toxicity may have a significant impact on a patient's quality of life (QOL), it is very important to attempt to reduce the adverse effects of treatment as much as possible (6).

We and others have previously reported that soy isoflavones exert anticancer effects (7–10) and enhance the efficacy of chemotherapy (11) and radiation therapy (12–17) in prostate cancer. Moreover, soy isoflavones have shown potent antioxidant and anti-inflammatory properties (18–21) and therefore could potentially protect normal adjacent tissues, thereby decreasing urinary, intestinal, and sexual adverse effects in patients receiving radiation therapy for prostate cancer. This pilot study was conducted to investigate if soy isoflavone supplementation during and after ERBT would alleviate urinary, intestinal, and sexual adverse effects of radiation therapy in patients with localized prostate cancer.

MATERIALS AND METHODS

Patients

The study protocol and consent were reviewed and approved by the Institutional Review Board of Wayne State University where the study was conducted. All patients signed a written informed consent prior to enrollment. Patients with histologically proven, localized prostate cancer who were scheduled to receive curative radiation therapy were eligible to participate in the study. Eligible patients had to be 18 yr or older with an ECOG performance status of 3 or less. To be eligible patients could not have been treated with previous or concurrent hormone therapy or chemotherapy. Patients were not allowed to take

concurrent vitamins, herbs, or micronutrients while they were on the study; but if they wished, they could take a single multivitamin daily.

Intervention

After signing the informed consent form, patients were randomly assigned to receive either soy isoflavone (200 mg) or placebo tablets. Tablets containing 50 mg soy isoflavones (Nova-soy) were provided by Archer Daniels Midland Company (Decatur, IL). Each tablet contained 50 mg of total soy isoflavones at a ratio of 1.1:1:0.2 for genistein:daidzein:glycitein, which account for 40% of total content of the tablet. Other contents of the tablets are soya saponins (30–40%), protein (9%), sugars (<1%), fat (<1%), and other minor soy components. Novasoy is an isoflavone-rich extract derived from soy and is classified as a nutritional or food product. Patients had to take two 50-mg Novasoy tablets twice daily (it could be taken in one dose or two divided doses with meals). The choice for the dose was based on our previous clinical study that showed a meaningful anticancer effect and lack of toxicity at this dose (10). Patients were instructed to take 2 tablets with breakfast and 2 tablets with dinner beginning with the first day of radiation. Patients were instructed to continue to take the study tablets for 6 mo in the absence of unacceptable toxicity.

Radiation Therapy

All patients underwent computerized tomography based simulation for radiation therapy planning. The volume of radiation included the prostate and seminal vesicles with a 1.5 cm margin. Patients received a total dose of 73.8 to 77.5 Gy photon radiation in 1.8 to 2.5 Gy fractions. The radiation was conformal and/or IMRT. Patients underwent daily BAT ultrasound localization or weekly port films.

QOL Questionnaires

The QOL questionnaires consisted of 50 questions at 3 mo or 53 questions at 6 mo; and the questions were related to potential urinary, bowel, and sexual side effects of radiation. Patients were provided these forms during their follow-up visits and were asked to return them upon completion. The questions focused on urinary symptoms, gastrointestinal symptoms, erectile function, and sexual function.

Patient Follow-Up

Patients had follow-up clinic appointments with the treating physician at 1 mo after completion of radiation treatment as well as at 3 mo and 6 mo from the start of therapy. At baseline, 3 mo, and 6 mo, history and physical exams were performed; QOL questionnaires were given; and peripheral venous blood was obtained for prostate-specific antigen (PSA), testosterone, CBC with differential and electrolytes. Toxicities were assessed using National Cancer Institute common toxicity criteria. No toxicities attributable to study tablets were noted, and no patients stopped taking their study tablets during study.

Analysis

Since this was a double-blind, randomized, placebo-controlled clinical trial, results were not analyzed, and the randomization code was not broken until after the study results were evaluated. Soy isoflavone and placebo tablets looked identical. After tabulating and analyzing all study results, the randomization code was broken to find out which group received soy isoflavone and which group received placebo. Compliance was 100% with the study tablets. However, only 62% of the subjects returned the study questionnaires. Therefore, no attempt was made for statistical analysis, which would be meaningless given

the very small number of events in each study arm. This study should be considered hypothesis-generating rather than hypothesis-testing.

RESULTS

Forty-two patients with localized prostate cancer were enrolled and treated between November 2002 and September 2006; 20 patients were randomly assigned to receive soy isoflavones, and 22 patients were assigned to placebo. The soy patients were designated as Group 1, and the placebo patients were designated as Group 2. Median ages were 60 and 65 for Groups 1 and 2, respectively. Despite repeated reminders, only 26 patients returned their 3-mo and 6-mo QOL questionnaires. Group 1 had 13 questionnaires returned for 3-mo and 6-mo evaluations, and Group 2 had 13 questionnaires returned for 3-mo visits and 14 questionnaires for 6-mo visits. Further data analysis was restricted to those subjects who returned their questionnaires.

Table 1 shows clinical characteristics of the study subjects. Tumor (T) stages were T1c (8 subjects), T2a (3 subjects), and T2b (2 subjects) in Group 1 ($n = 13$) and T1c (10 subjects), T2a (2 subjects), and T2b (1 subject) in Group 2 ($n = 13$). All patients had Gleason score of 6 except two patients with Gleason score of 7 in Group 2. Patients in Group 1 had T1c ($n = 8$), T2a ($n = 3$), and T2b ($n = 2$) tumors; and their median age was 60. Tumor stages for Group 2 consisted of T1c ($n = 10$), T2a ($n = 2$), and T2b ($n = 1$); and their median age was 65. Median pretreatment serum PSA levels were 3.7 ng/ml (Group 1) and 4.9 ng/ml (Group 2). After radiation, therapy PSA levels were repeated between 3 and 6 mo, which showed a decline in the median PSA by 75.7% in Group 1 (to 0.9 ng/ml) and by 59.2% in Group 2 (to 2.0 ng/ml).

Table 2 shows the adverse effects of radiation in soy isoflavone and placebo groups at 3 mo and 6 mo. At 3 mo, there was less dripping and/or leakage of urine (15.4% vs. 23.1%) and less problems with medium and/or big urgency (0% vs. 30.8%) in Group 1 compared to Group 2 (Table 2). Gastrointestinal symptoms were similar in both groups. Erectile function was better in Group 1 in all respects. There was better overall ability to have erections (69.2% vs. 61.5%), less reduction in the ability to have erections (15.4% vs. 46.2%), and more men had erectile function the same as or better than baseline (before radiation therapy) compared to Group 2 (84.6% vs. 61.5%).

At 6 mo, there was less dripping and/or leakage of urine (7.7% vs. 28.4%), less rectal cramping and/or diarrhea (7.7% vs. 21.4%), and less pain with bowel movements (0% vs. 14.8%) in Group 1 compared to Group 2 (Table 2). Compared to Group 2, Group 1 had better overall ability to have erections (77% vs. 57.1%), lower reduction in the ability to have erections (15.4% vs. 57.1%), and more men with erectile function the same or better than baseline function (84.6% vs. 57.1%; Table 2).

DISCUSSION

Epidemiologic studies have shown an inverse association between soy consumption and prostate cancer risk (22). Isoflavones found in soybeans include genistein, daidzein, and glycitein; and these compounds have been postulated and demonstrated to be the principal biologically active anticancer ingredients (8, 9). Various mechanisms may be important for the activity of soy isoflavones in prostate cancer, including their antiestrogen or estrogen-like effects, antioxidant effects, anti-inflammatory effects, antiangiogenic effects, and other inhibitory effects on cancer cell growth and metastasis (8–11).

We have previously observed that soy isoflavones potentiated the effects of radiation against prostate cancer cells in vitro and in vivo in orthotopic murine models (12–17). Along with this treatment-potentiating effect on cancer, it is possible that the antioxidant properties of soy isoflavones could play a role in protecting normal tissues, which are exposed to radiation. Although some antioxidant micronutrients could theoretically also protect the tumor from radiation, which would not be desirable, in our in vivo studies, we have observed only enhancement of antitumor effect of radiation when soy isoflavones were administered in conjunction with radiation and no protection of cancer against radiation's antitumor effect (16, 17).

Acute and subacute toxicities from EBRT for prostate cancer are well known. They primarily include urinary and intestinal adverse effects and erectile dysfunction. Although EBRT is generally well tolerated, its acute toxicity could be significant in 5–10% of patients (3, 4). The results from this pilot study in locally advanced prostate cancer patients suggest that soy isoflavones taken in conjunction with EBRT may reduce the urinary, intestinal, and sexual adverse effects observed in these patients. It would take years of follow-up and a much larger number of patients to determine if the efficacy of EBRT is enhanced and the cancer relapse rate is reduced by the addition of concurrent soy isoflavones to treatment. However, PSA is a good surrogate end point for prostate cancer, and the levels of pretreatment and posttreatment PSA in this study suggest that the efficacy of the radiotherapy is not reduced by concurrent administration of soy isoflavones; if anything, the results look better in the soy arm.

Patients receiving soy isoflavones during and after EBRT showed decreased incidence of urinary, gastrointestinal, and erectile dysfunction when compared to those patients receiving placebo. Overall, 7–31% of patients in the placebo group had acute urinary toxicity, and 7–21% had acute intestinal toxicity. Although our sample size is very small, other series have shown similar rates of acute toxicity. Pinkawa et al (23) treated 204 men with >70 Gy EBRT and assessed side effects at completion of treatment as well as at 2 and 12 mo thereafter. One-third of men reported dysuria, and 37% reported obstructive symptoms at completion of treatment. There was also increased bowel toxicity and erectile dysfunction at 2 mo postradiation.

Soy isoflavones have been reported to have efficacy in patients with biochemical recurrence after surgery or radiation (10, 24). Research studies performed in vitro that have used human prostate cancer PC3 and C4-2B cells showed a greater inhibition of cell growth when cells were treated with pure genistein or a mixture of soy isoflavones combined with radiation compared with each modality alone (12,14,15,17,25,26). The role of genistein or soy as a radiosensitizer has also been investigated in syngeneic and xenograft prostate cancer orthotopic murine models (13,16,17). These studies have shown a significant inhibition of tumor growth both in the primary prostate tumor and lymph node metastasis when soy isoflavones were administered in conjunction with prostate tumor irradiation.

The antioxidant (18,27–31) and anti-inflammatory (21,31) activities of soy isoflavones have previously been reported. Kapiotis (27) has shown that genistein was able to inhibit the oxidation of LDL in the presence of copper ions or superoxide/nitric oxide radicals as measured by thiobarbituric acid-reactive substance formation, alteration in electrophoretic mobility, and lipid hydroperoxides. Other studies have shown that genistein reduced the prothrombotic phenotype of endothelial cells, further substantiating and explaining the beneficial effects of dietary genistein in preventing atherosclerosis and related vascular events (29). Researchers from Finland also presented similar results showing that intake of soy-derived antioxidants, such as genistein and daidzein, may provide protection against oxidative modification of LDL (30). Since tissue toxicities of radiation are due to oxidation-

induced vascular changes and inflammation, the antioxidant and anti-inflammatory effects of soy isoflavones could play a role in the prevention of radiation toxicities. We have also observed amelioration of radiation toxicity with lycopene, another potent antioxidant agent with significant activity in prostate cancer (32,33), which lends further support to the hypothesis that certain nutritional agents such as soy isoflavones and lycopene could be added to radiation to enhance the efficacy and reduce the toxicity of radiotherapy.

In summary, the results of our pilot study suggest that the adverse effects of EBRT could be ameliorated by administration of soy isoflavones in patients with prostate cancer. The strengths of this clinical trial are its double-blind, placebo-controlled, randomized nature; good compliance with the study tablets; and the use of study tablets with known bioavailability, safety, and efficacy in prostate cancer patients (10). Its weaknesses are the small number of subjects and the poor compliance rate with self-administered study questionnaires. In future studies, study coordinators should assist patients with the administration of study questionnaires to ensure better compliance. Because of the small numbers of subjects in each arm of the study and very small number of adverse events in each subgroup, these results are considered hypothesis generating and not hypothesis testing. Larger clinical trials are warranted to investigate the potential amelioration of radiation toxicity and potential enhancement of radiation efficacy with soy isoflavones in patients with prostate cancer.

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TABLE 1Patient clinical characteristics^a

Variable	Group 1 (Soy Isoflavone)	Group 2 (Placebo)
Age, yr		
Median	60	65
Disease stage (TNM)		
T1c	8	10
T2a	3	2
T2b	2	1
Pre-PSA		
Median	3.7	4.9
Post-RT PSA		
Median: 4–6 mo	0.9	2
PSA reduction		
Pre-vs. post-RT	75.70%	59.20%

^a Abbreviations are as follows: TNM, tumor, node, metastasis staging classification; T, tumor; PSA, prostate specific antigen; RT, radiation therapy.

TABLE 2Decreased adverse effects of radiation therapy by soy isoflavones^a

Variable	3 Mo		6 Mo	
	Soy (n = 13)	Placebo (n = 13)	Soy (n = 13)	Placebo (n = 13)
Genitourinary effects				
Leakage or dripping of urine	15.4%(2)	23.1%(3)	7.7%(1)	28.6%(4)
Big/medium problem with frequency	38.5%(5)	38.5%(5)	0%	7.1%(1)
Big/medium problem with urgency	0%	30.8%(4)	0%	0%
Function same as before RT or better	92.3%(12)	92.3%(12)	92.3%(12)	85.7%(12)
Gastrointestinal effects				
Cramping or diarrhea	15.4%(2)	7.7%(1)	7.7%(1)	21.4%(3)
Big/medium pain with bowel movements	7.7%(1)	0%	7.7%(1)	14.3%(2)
Erectile function				
Ability to have full erections	69.2%(9)	61.5%(8)	77% (10)	57.1%(8)
Reduction in ability to have erections	15.4%(2)	46.2%(6)	15.4%(2)	57.1%(8)
Function same as before RT or better	84.6%(11)	61.5%(8)	84.6%(11)	57.1%(8)

^a Abbreviation is as follows: RT, radiation therapy.