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Original article

A prospective clinical trial of green tea for hormone refractory prostate cancer: An evaluation of the complementary/alternative therapy approach

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Abstract

Purpose: To evaluate the efficacy and toxicity of green tea, prescribed as an alternative complementary (CAM) formulation on hormone refractory prostate cancer (HRPC).

Methods: Patients with HRCP were prescribed green tea extract capsules at a dose level of 250 mg twice daily. Efficacy and toxicity were evaluated during monthly visits. The primary endpoint was prostate-specific antigen (PSA) or measurable disease progression after a minimum of 2 months of therapy.

Results: Nineteen patients were enrolled into the study. The treatment was generally well tolerated. Twelve patients reported at least one side effect; only two of these were of moderate or severe grade. Primary toxicity was related to gastrointestinal irritation or caffeine intake. Four patients did not complete the minimum 2 months of therapy because of: intolerance (two patients), physician stoppage (one patient), death from cerebrovascular accident (one patient). Fifteen patients completed at least 2 months of therapy. Nine of these patients had progressive disease within 2 months of starting therapy. Six patients developed progressive disease after additional 1 to 4 months of therapy.

Conclusion: Green tea, as CAM therapy, was found to have minimal clinical activity against hormone refractory prostate cancer.

1. Introduction

The use of alternative and complimentary (CAM) therapy in the prostate cancer population has become very popular [1–3] despite the paucity of clinical data to demonstrate its efficacy. One study has reported that up to 43% of patients in this group utilize CAM at some time during the course of their disease [1].

Nutritional supplements, such as green tea, have become a common class of CAM therapy utilized by patients with prostate cancer. Their popularity has been fueled by laboratory data suggesting that their extracts contain anticancer agents [4–8].

The biochemical mechanisms whereby green tea exerts its antineoplastic effect has been well studied in vitro and in animal studies. Biochemical analyses confirm that green tea contains polyphenols compounds that have been shown to possess strong antioxidant activity. EGCG (epigallocatechin-3-gallate), the major polyphenol found in green tea, has been shown to render significant activity in animal models, protecting against all stages of carcinogenesis, including initiation, promotion and progression [4–6]. Additionally, other studies have also shown that green tea extracts and EGCG can inhibit the growth of skin and sarcoma cell lines in animal models [7,8]. In vitro studies utilizing prostate cancer cell lines confirm that EGCG inhibits the growth of hormone sensitive as well hormone-insensitive clonogens [9,10].

The molecular mechanism of green tea's anticancer activity is currently being elucidated. Polyphenols target multiple pathways that alter apoptosis, cell growth and angiogenesis [9–12]. Ongoing research is directed towards defining novel pathways that may be modulated by green tea or its active constituents [13].

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Despite the wealth of laboratory data, there is no clinical data proving its clinical efficacy against prostate cancer [14,15]. With so many patients utilizing CAM-such as green tea, mostly without medical supervision there appears to be a need for critical evaluation of these products for efficacy and safety.

Green tea's popularity, its intriguing preclinical data, and the lack of clinical proof of efficacy were the impetus for this clinical trial. This study was designed to evaluate the toxicity and clinical response rate of commercially available green tea extracts against hormone refractory prostate cancer. We evaluated the effect of the consumption of the generally recommended dose of green tea on objective measures of prostate cancer activity.

2. Methods

2.1. Study design

This is a single institutional prospective single arm clinical trial conducted at the Ottawa Hospital Regional Cancer Centre. This trial was reviewed and approved by the Institutional Review Board of The Ottawa Hospital.

2.2. Patient eligbility

Patients with hormone refractory prostate cancer were eligible for study entry. Eligibility criteria were as follows: (1) Absolute prostate-specific antigen (PSA) $\geq$ 10 ng/mL; (2) progessive disease as defined by a minimum of three consecutive rises of PSA over a period of at least 2 months, or evidence of radiologic progression; (3) testosterone suppression with either bilateral orchiectomy or leutinizing hormone releasing hormone analogue; (4) progressive disease while on a nonsteroidal antiandrogen or progressive disease during its withdrawal; (5) no bisphosphonate therapy or progessive disease on bisphosphonate therapy; (6) no cytotoxic chemotherapy within 2 months of study entry; (7) life expectancy $\geq$2 months; (8) not consuming alternative or complementary therapy within 4 weeks of study entry; (9) not allergic to green tea; (10) New York Heart Association Functional Classification Class I or II; (11) No history of palpitations, arrhythmias, hyperthyroidism, panic or anxiety disorder; (12) Serum AST, ALT, ALP $\leq$2$\times$ normal; (13) serum creatinine $\leq$200 μmol/L.

2.3. Baseline evaluation

All eligible patients underwent a baseline assessment that included: (1) a history and physical examination including a digital rectal examination, (2) complete blood count, (3) serum liver enzyme levels, (4) serum PSA and total testosterone levels, (5) whole body bone scan, (6) toxicity score.

2.4. Treatment

There is a range of recommended doses for the green tea products available to the Canadian public. At the inception of this study, a survey of the retail market revealed that the recommended daily dose of green tea ranged from 50 to 1800 mg, containing between 30 to 300 mg of polyphenols. As green tea was marketed as a nutritional supplement, not as a drug, there was no specific recommended daily dose for the treatment of prostate cancer.

Patients in this study were prescribed capsules of green tea extract, produced and provided by Sabinsa Corporation (Piscataway, NJ), at a dose of 250 mg twice daily. The decaffeinated extracts contain less than 2% caffeine and greater than 75% polyphenols, of which greater than 30% is EGCG. The daily dose of caffeine for the prescribed dose in the study was 1 mg whereas the daily intake of polyphenols was 375 mg. The dose selected for the study was chosen to reflect the highest availability of the purported active ingredients, polyphenols, available to the Canadian public from green tea retailers.

2.5. Treatment evaluation

All patients were seen monthly for the duration of the study. At each visit, each patient underwent the following: (1) a history and physical, including the documentation of the performance status, toxicity, weight and rectal exam; (2) serum PSA, total testosterone, creatinine and liver enzyme level testing.

A whole body bone scan was to be performed bimonthly. Plain X-rays and computed tomography (CT) scans were also performed bimonthly if there were documented abnormalities at study entry. Treatment compliance, as documented by medication diaries, was recorded at each visit.

2.6. Toxicity evaluation

Side effects were reported by the attending physician at each monthly visit. In addition, patients recorded their experienced side effects on a self-reporting form at each visit.

2.7. Endpoints and statistics

The primary endpoint of this study was disease progression as defined by either (1) a relative PSA rise of greater than 25% over baseline over a 2-month period, or (2) evidence of radiologic progression. Radiologic progression was defined as either a greater than 25% increase in the product of the two largest dimensions of measurable disease on CT scan, or a discernible increase in the number or intensity of abnormal bone activity on the bone scan, as reported by the radiologist.

The target accrual for the study was 35 patients. The target number of evaluable patients for the study was 30 patients. The additional five patients targeted for accrual is

Table 1
Baseline patient characteristics

Age (years)	Median	76
	Range	61–84
Baseline PSA (ng/mL)	Median	161
	Range	8.5–588
Radiologic disease (patients)	Bone scan positive	15
	Bone scan negative	4
Extent of disease on bone scan	Few lesions	5
	Multiple	7
	Extensive	3
Prior therapy (patients)	Radical radiotherapy	5
	Chemotherapy	4
Karnofsky PS	Median	90
	Range	70–100

factored in for those patients who may be deemed ineligible for evaluation at the end of the study.

The target number of evaluable patients was derived using a *t*-test formulation. The target accrual figure provides a 95% level of confidence that the true response rate is no greater than 20% if the study showed a control rate of 10%. Conversely, if the control rate in the study was found to be greater than 30%, there would be a 95% level of confidence that the true response rate is no less than 14%.

An unscheduled interim analysis was performed after the publication of the Jatoi et al. study [15]. The unequivocally negative result of that study was the impetus of the interim analysis. This study was closed to enrollment when the interim analysis revealed that there is only a remote statistical probability that this trial will produce a meaningful positive outcome.

3. Results

3.1. Accrual

A total of 36 patients were approached to enter the study. Ten patients elected to not enter the study and seven patients were deemed ineligible.

3.2. Baseline characteristics

A total of 19 patients were enrolled into the study. The median age was 76 yr. Median Karnofsky performance status was 90, with a range of 70 to 100. The median baseline PSA level was 161 ng/mL, with a range from 8.53 to 588 ng/mL. Fifteen patients had metastatic disease to the bones, as demonstrated on nuclear bone scans. Ten of these patients had multiple or extensive foci of disease activity whereas five were found to have a few areas of disease activity. Most patients were not symptomatic from their bone disease; only three patients reported a mild degree of pain. Four patients had received chemotherapy before study entry. Five patients had undergone prior radical (potentially curative) radiotherapy for their prostate cancers (Table 1).

3.3. Toxicity

Symptoms that appeared subsequent to the initiation of therapy are summarized in Table 2. A total of 12 patients reported at least one symptom. Five patients reported gastro-intestinal symptom(s), two patients reported symptoms related to caffeine intake and five additional patients reported symptoms that may be attributable to green tea consumption. These side effects from green tea intake were mild in all but two cases. One patient reported severe anorexia and another reported a moderate degree of dyspnea. Other reported symptoms, including bony pain, impotence, incontinence and hot flashes, were attributed to progressive prostate cancer or androgen ablation therapy.

Two patients elected to stop their treatment after 3 and 10 days because of intolerance. One patient passed away from a cerebrovascular accident after 6 weeks of therapy. The death was not attributed to the green tea.

3.4. Efficacy

Table 3 summarizes the status of the patients at the end of the study. Of the 19 patients that entered the study, there were four patients whose treatments were stopped prematurely: two patients decided to stop because of intolerance, one patient died within 6 weeks of study entry with, but not of, progressive disease, and one patient had his treatment discontinued at 1 month by the treating physician for progressive disease.

Of the 15 patients who consumed green tea for at least 2 months, nine patients had progressive disease within 2 months of starting therapy. The other six patients had pro-

Table 2
Symptoms reported during study

	Total number of patients
GI irritation	
Abdominal discomfort	2
Anorexia	1
Heartburn	1
Nausea	1
Diarrhea	2
Caffeine intake	
Insomnia	1
Palpitations	1
Possibly related to green tea	
Muscle cramps	1
Nocturia	1
Dyspnea	2
Fatigue	3
Headache	1
Hypertension	1
Disease related	
Malaise	1
Pain	4
Androgen ablation	
Hot flushes	4
Impotence	1

Table 3
Status of patients at the end of study

2 Mos of Rx	Status at the end of study	Duration of Rx	# Patients
<2 mos	Died with PSA progression	6 wks	1
	Doctor stopped Rx, PSA and local progression	4 wks	1
	Patient decided to stop d/t toxicity	3 days	1
	Patient decided to stop d/t toxicity	10 days	1
≥2 mos	PSA progression	2 mos	7
	PSA progression	3 mos	3
	PSA progression	4 mos	1
	PSA progression	5 mos	1
	Radiologic progression	2 mos	1
	Radiologic and PSA progression	2 mos	1
	Radiologic and PSA progression	3 mos	1
		Total	19

gressive disease within three to 5 months of starting therapy. For these patients, their PSA levels were relatively flat for the first 1 to 4 months on treatment. An examination of their PSA profiles before and after therapy revealed that there was a modest deceleration of the PSA rise in only one of these six patients, lasting for approximately 2 months. This patient developed progressive nodal disease despite a modest decrease in his PSA.

The profile of each patient's PSA is represented in graphical form in Fig. 1. As per our definition of disease progression, there was an apparent slowing of disease progression in 6 of 15 patients while on this study, lasting 1 to 4 months. Inspection of their PSA profiles before and after therapy revealed that the PSA rise was discernibly slowed in only one of these six patients. There were no responders as per the traditional definition of a PSA drop of greater 50% from baseline.

4. Discussion

This study was designed to evaluate the effect of green tea consumption on the clinical course of progressive hormone refractory prostate cancer. The dose of green tea tested reflected the range of doses available to consumers in the retail market.

There was a high level of willingness to participate in this study amongst the patients approached. Out of 36 pa-

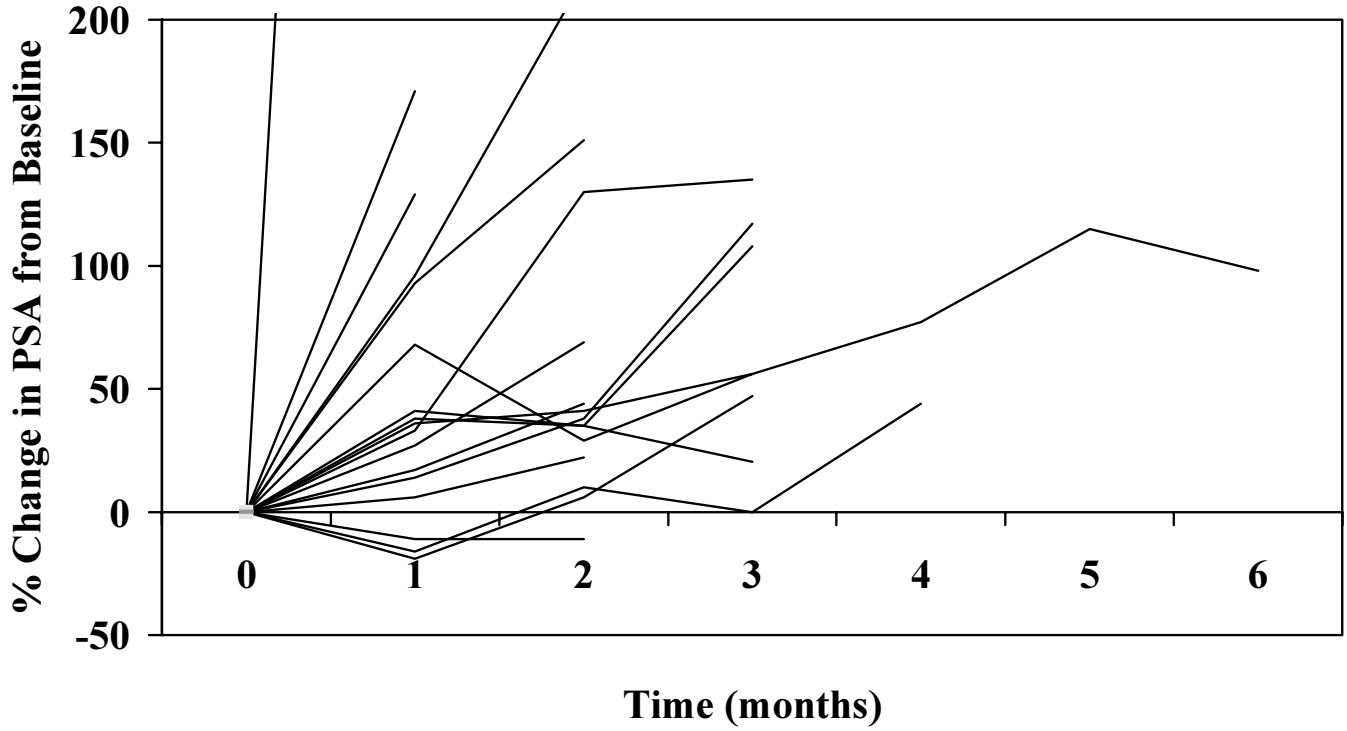

Fig. 1. PSA profile for each study patient.

tients approached, 26 patients agreed to enter the study. This relatively high rate of acceptance most likely reflects the commonly held view that alternative therapies are generally safe, and hold some promise of efficacy.

The green tea was generally well tolerated. Most symptoms were reported as mild, with only three reports of moderate or severe side effects arising from two patients. Symptoms were usually related to caffeine intake and gastrointestinal irritation. Two other studies, by Pisters [14] and Jatoi [15] also found similar types of side effects from significantly higher doses of green tea. At a dose of 6 g of green tea per day, Jatoi found six episodes of Grade 3 and one episode of Grade 4 toxicity out of 42 treated patients.

Our study revealed that green tea, within the dosage range available for general consumption, does not discernibly alter the course of hormone refractory prostate cancer. Although, technically, there were 6 out of 19 patients who achieved disease control for 3 to 5 months, there was only one patient whose PSA rise was discernibly affected by green tea consumption and no patient had achieved a significant reduction in his PSA with the therapy.

Our results are in agreement with those of the study by Jatoi et al [15]. In their study, only one out of 42 patients had a response to therapy, as defined by a >50% decline in PSA from baseline. The most significant difference between this and Jatoi's study is the dose of green tea prescribed. Jatoi's study was designed as a traditional Phase II study, in follow-up to Pisters' Phase I study [14] showing the maximum tolerable daily dose of green tea to be 4.2 g/m^2 once daily. In contrast, our study was designed to evaluate green tea as a CAM therapy. The impetus for this study was to provide some clinical data on a nonmedical therapy that is commonly used by the public.

Despite green tea's promising and intriguing body of preclinical data suggesting its anticancer activity, its clinical validation has yet to be produced. There are two obvious explanations for this discordance. First, the two clinical trials, by Jatoi [15] and E, both enrolled patients with progressive, advanced prostate cancers. Both studies targeted patients with hormone refractory prostate cancer. In our study, 15 of 19 patients had documented metastatic disease, while the median PSA was 161 ng/mL. In Jatoi's study, the mean PSA was 583 ng/mL, with 33% of the patients had undergone prior chemotherapy [15]. These cancers have typically had many years to develop aggressive, resistant behavior; as is evidenced by their escape from conventional therapy. Adolfsson and Tribukait [16] have illustrated this phenomenon with their elegant study of serial biopsies of untreated prostate cancers. It was found that, during the course of the study, untreated prostate tumors acquired genomic changes and cytologic transformations; supporting the concept of gradual dedifferentiation of the tumor over time. It is perhaps unrealistic to expect the ingestion of whole green tea to induce a clinical response in these advanced prostate cancers.

Secondly, it would appear that therapeutic serum concentrations of EGCG are not achievable with the oral route of administration. In Pisters' study [14], the maximum serum level of EGCG was found to be 100 to 225 ng/mL, between 1 and 3 h after single dose administrations of 2.2 to 4.2 g/m^2 of green tea. For those with the 1 g/m^2 twice-daily dosage, the peak serum levels were considerably lower. The serum EGCG concentration decreased over the course of hours, without any time-dependent accumulation over a period of 8 weeks. No tumor responses were seen in their study. In comparison, Paschka [10] exposed prostate cancer cell lines, in vitro, to varying concentrations of EGCG (mw = 458) continuously over the course of 6 days. At concentrations of 10 μM (4580 ng/mL) or higher, EGCG showed evidence of growth inhibition of the androgen-independent cell line. In another study, Ahmad et al. [11] exposed DU145 prostate cancer cell lines to 80 μg/mL (80,000 ng/mL) of EGCG for 48 h to induce apoptosis. These laboratory studies exposed their cell lines to concentrations of EGCG that are at least an order of magnitude higher than what was achieved in the clinical study using the maximal daily dosage of green tea. It appears unlikely that the oral intake of green tea can produce adequate levels of serum EGCG for the inhibition of prostate cancer growth. To achieve higher serum concentrations of EGCG, a purified form may need to be delivered, either orally or parenterally.

With respect to the consumption of whole green tea for hormone refractory prostate cancer, the accumulated clinical evidence would suggest that there is little promise of anticancer activity for this clinical indication. Future clinical research may focus on the prescription of the active compound(s) in green tea, either orally or parenterally. Additionally, green tea's role in the prevention and early disease progression of prostate cancer require further investigation and evaluation. Use of this agent as a chemopreventative agent holds the greatest potential for clinical benefit.

In conclusion, this study revealed that green tea, as prescribed in an alternative/complementary manner, produced no discernible clinical activity against hormone refractory prostate cancer. The green tea was well tolerated and there was a high level of acceptance in patients approached to enter the study.

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References

[1] Lippert MC, McLain R, Boyd JC, et al. Alternative medicine use in patients with localized prostate carcinoma treated with curative intent. Cancer 1999;86:2642–8.

[2] Nam RK, Fleshner N, Rakovitch E, et al. Prevalence and patterns of the use of complementary therapies among prostate cancer patients: an epidemiologic analysis. J Urol 1999;161:1521–4.
[3] Jacobson JS, Chetty AP. Complementary and alternative medicine in prostate cancer. Curr Oncol Rep 2001;3:448–52.
[4] Katiyar SK, Agarwal R, Mukhtar H. Protection against malignant conversion of chemically induced benign skin papillomas to squamous cells carcinomas in SENCAR mice by a polypehnolic fraction isolated from green tea. Cancer Res 1993;53:5409–12.
[5] Xu Y, Ho CT, Amin SG, et al. Inhibition of tobacco specific nitrosamine-induced lung tumorigenesis in A/J mice by green tea and major polyphenol as antioxidants. Cancer Res 1992;52:3875–9.
[6] Gensler HL, Timmermann BN, Valcic S, et al. Prevention of photocarcinogenesis by topical administration of pure epigallocatechin gallate isolated from green tea. Nutr Cancer 1996;26:325–35.
[7] Katiyar SK, Mukhtar H. Tea in chemoprevention of cancer: epidemiological and experimental studies (Review). Intl J Oncol 1996;8: 221–38.
[8] Yang CS, Wang ZY. Tea and cancer. J Natl Can Inst 1993;85:1038–49.
[9] Liao S, Umekita Y, Guo J, et al. Growth inhibition and regression of human prostate and breast tumors in athymic mice by tea epigallocatechin gallate. Cancer Lett 1995;96:239–43.
[10] Paschka AG, Butler R, Young CY. Induction of apoptosis in prostate cancer cell lines by the green tea component, (-)- epigallocatechin-3-gallate. Cancer Lett 1998;130:1–7.
[11] Ahmad N, Feyes DK, Nieminen AL, et al. Green tea constituent epigalocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. J Natl Cancer Inst 1997;89:1881–6.
[12] Lamy S, Gingras D, Beliveau R. Green tea catechins inhibit vascular endothelial growth factor receptor phosphorylation. Cancer Res 2002; 62:381–5.
[13] Adhami VM, Ahmad N, Mukhtar H. Molecular targets for green tea in prostate cancer prevention. J Nutr 2003;133(suppl.):2417S–24S.
[14] Pisters KM, Newman RA, Coldman B, et al. Phase I trial of oral green tea extract in adult patients with solid tumors. J Clin Oncol 2001;19: 1830–8.
[15] Jatoi A, Ellison N, Burch PA, et al. A phase II trial of green in the treatment of patients with androgen independent metastatic prostate cancer. Cancer 2003;97:1442–6.
[16] Adolfsson J, Tribukait B. Evaluation of tumor progression by repeated fine needle biopsies in prostate adenocarcinoma: modal deoxyribonucleic acid value and cytological differentiation. J Urol 1990;144:1408–10.