A Phase II Trial of Green Tea in the Treatment of Patients with Androgen Independent Metastatic Prostate Carcinoma

Aminah Jatoi, M.D.[1]
Neil Ellison, M.D.[3]
Patrick A. Burch, M.D.[1]
Jeff A. Sloan, Ph.D.[1]
Shaker R. Dakhil, M.D.[4]
Paul Novotny, M.S.[3]
Winston Tan, M.D.[2]
Tom R. Fitch, M.D.[5]
Kendrith M. Rowland, M.D.[6]
Charles Y. F. Young, Ph.D.[1]
Patrick J. Flynn, M.D.[7]

[1] Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

[2] Mayo Clinic and Mayo Foundation, Jacksonville, Florida.

[3] Geisinger Clinic and Medical Center Community Clinical Oncology Program, Danville, Pennsylvania.

[4] Wichita Community Clinical Oncology Program, Wichita, Kansas.

[5] Mayo Clinic and Mayo Foundation, Scottsdale, Arizona.

[6] Carle Cancer Center Community Clinical Oncology Program, Urbana, Illinois.

[7] Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, Minnesota.

This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic and was supported in part by Public Health Service grants CA-25224, CA-37404, CA-15083, CA-63826, CA-35448, CA-60276, CA-35195, CA-37417, CA-35113, CA-52352, and CA-35415.

Additional participating institutions include: Meritcare Hospital Community Clinical Oncology Program (CCOP), Fargo, ND (Ralph Levitt, M.D.); Illinois Oncology Research Association CCOP, Peoria, IL (John W. Kugler, M.D.); Medcenter One Health Systems, Bismarck, ND; Mid Dakota Clinic, Bismarck, ND (Ferdinand Addo, M.D.); Cedar Rapids Oncology Project CCOP, Cedar Rapids, IA (Martin Wiesenfeld, M.D.); and Toledo Community Hospital Oncology Program CCOP, Toledo, OH (Paul L. Schaefer, M.D.).

Address for reprints: Aminah Jatoi, M.D., Mayo Clinic, 200 First Street, SW, Rochester, MN 55905; Fax: (507) 284-1803; E-mail: jatoi.aminah@mayo.edu

Received October 15, 2002; revision received October 15, 2002; accepted October 28, 2002.

BACKGROUND. Recent laboratory and epidemiologic studies have suggested that green tea has antitumor effects in patients with prostate carcinoma. This Phase II trial explored green tea's antineoplastic effects in patients with androgen independent prostate carcinoma.

METHODS. This study, which was conducted by the North Central Cancer Treatment Group, evaluated 42 patients who were asymptomatic and had manifested, progressive prostate specific antigen (PSA) elevation with hormone therapy. Continued use of luteinizing hormone-releasing hormone agonist was permitted; however, patients were ineligible if they had received other treatments for their disease in the preceding 4 weeks or if they had received a long-acting antiandrogen therapy in the preceding 6 weeks. Patients were instructed to take 6 grams of green tea per day orally in 6 divided doses. Each dose contained 100 calories and 46 mg of caffeine. Patients were monitored monthly for response and toxicity.

RESULTS. Tumor response, defined as a decline $\geq$ 50% in the baseline PSA value, occurred in a single patient, or 2% of the cohort (95% confidence interval, 1–14%). This one response was not sustained beyond 2 months. At the end of the first month, the median change in the PSA value from baseline for the cohort increased by 43%. Green tea toxicity, usually Grade 1 or 2, occurred in 69% of patients and included nausea, emesis, insomnia, fatigue, diarrhea, abdominal pain, and confusion. However, six episodes of Grade 3 toxicity and one episode of Grade 4 toxicity also occurred, with the latter manifesting as severe confusion.

CONCLUSIONS. Green tea carries limited antineoplastic activity, as defined by a decline in PSA levels, among patients with androgen independent prostate carcinoma. ***Cancer* 2003;97:1442–6.** *© 2003 American Cancer Society.*
DOI 10.1002/cncr.11200

KEYWORDS: alternative therapy, epigallocatechin-3-gallate, green tea, polyphenols, prostate carcinoma, toxicity.

Brewed after steaming the leaves of the *Camellia sinensis* plant, green tea is widely consumed throughout the world. Recent laboratory and epidemiologic studies suggest that it carries antineoplastic effects in patients with prostate carcinoma. At the same time, surveys suggest that patients with malignant disease frequently resort to nonprescription (or so-called *alternative*) therapies like green tea because of such purported antitumor effects. A recent survey by Nam

et al. found that > 25% of patients with prostate carcinoma use these alternative therapies,[1] whereas other studies suggest this prevalence rate is even higher.[2]

The preclinical data for green tea as an antineoplastic agent in patients with prostate carcinoma are provocative. Green tea contains a variety of polyphenols, which induce apoptosis and inhibit tumor growth in vitro in androgen independent prostate carcinoma. The cell lines LNCaP, PC-3, and DU145 all have demonstrated apoptosis and growth inhibition after exposure to epigallocatechin-3-gallate, the most prevalent polyphenol in green tea.[3] More recently, Gupta et al. examined the effects of green tea in a tumor model that closely resembles human prostate carcinoma, otherwise known as transgenic adenocarcinoma of the mouse prostate (TRAMP).[4] When green tea was administered orally to mice with TRAMP, not only did their overall incidence of tumor development decline, but these tumor-bearing animals demonstrated a decreased tumor burden and a decreased incidence of distant metastases compared with a control group. Although mechanisms that explain these potential antineoplastic effects have not been elucidated fully, the foregoing data suggest that green tea merits further study in a clinical setting.

Epidemiologic studies also have suggested that green tea may have antitumor affects against carcinoma of the prostate. Not all of those trials specifically examined prostate carcinoma risk, and not all specifically examined green tea. Nonetheless, those studies reported provocative findings. In a prospective study of 8552 individuals, Imai et al described a lower incidence of malignant disease in general among avid drinkers of green tea, thereby further suggesting that green tea may affect tumor growth or development.[5] Jain and colleagues reported on a case–control study that examined the association of beverage intake and the risk of prostate carcinoma.[6] Examining 617 patients with prostate carcinoma and 637 control participants (individuals without prostate carcinoma), those investigators found a slightly decreased risk of prostate carcinoma with tea intake (not specifically green tea) of more than 500 grams per day, as measured in fluid weight (odds ratio, 0.70; 95% confidence interval, 0.50–0.99). Studying black tea, a more oxidized form of tea, Heilbrun et al. reported a significant, inverse correlation between tea consumption and prostate carcinoma risk.[7] Coupled with the laboratory data discussed above, these epidemiologic studies suggest that green tea plays an antitumor role in patients with prostate carcinoma.

The current Phase II clinical trial was designed to build on such preclinical and epidemiologic data and on patients' proclivities for resorting to such *alternative* medicine approaches. Because patients with androgen independent prostate carcinoma face limited treatment options as well as a limited life expectancy, this trial was designed to explore whether green tea may offer an effective treatment strategy for this group of patients. The main objective of this trial was to determine the percentage of patients with asymptomatic, androgen independent prostate carcinoma who sustain a decline in prostate specific antigen (PSA) level after ingesting a highly concentrated form of green tea. Such data would allow us to determine whether green tea merits continued investigation as an antineoplastic agent among patients with androgen independent prostate carcinoma.

MATERIALS AND METHODS

Overview

This multiinstitutional, Phase II trial was conducted within the North Central Cancer Treatment Group, and all 22 cooperative group sites participated. The Institutional Review Board (IRB) of the Mayo Clinic in Rochester, Minnesota approved this trial along with the Institutional Review Boards at all of the other treatment sites.

Patient Eligibility

Eligible patients had asymptomatic prostate carcinoma, biopsy-proven evidence of malignancy, and clinical evidence of androgen independent disease. Androgen independence was defined as disease progression after undergoing orchiectomy, during treatment with luteinizing hormone-releasing hormone (LHRH), or after initiation of another hormonal agent. When tumor progression was defined on the basis of PSA increase, criteria from the Prostate Specific Antigen Working Group were provided to determine patient eligibility;[8] such criteria were inserted verbatim into the protocol.

Other eligibility criteria included the following: 1) no other anticipated treatment for prostate carcinoma within the next 2 months, although patients were allowed to continue on LHRH agonists; 2) physician-estimated life expectancy $\geq$ 3 months; 3) Eastern Cooperative Oncology Group performance status $\geq$ 2; 4) patient age $\geq$ 18 years; 5) serum creatinine $\leq$ 2 times the reference laboratory's upper normal limit; and 6) serum total bilirubin $\leq$ 1.5 mg/dL. Finally, if patients had received antiandrogen therapy in the past, then this therapy must have been discontinued $\geq$ 4 weeks prior to study enrollment or, in patients who received longer acting agents, $\geq$ 6 weeks prior to enrollment. Patients were deemed ineligible for trial participation if they had 1) received any treatment for malignant disease other than an LHRH agonist within the past 4

weeks; 2) a notable history of heart disease or diabetes; 3) central nervous system metastases; or 4) another malignancy within the past 5 years other than basal cell carcinoma of the skin.

Treatment Plan and Test Schedule

All patients were prescribed green tea at a dose of 6 grams per day (generously provided by Unilever, Englewood Cliffs, NJ). This dose was based in part on previous Phase I testing from Pisters et al.[9] Tea was administered in canisters and consisted of pulverized green tea powder as well as sugar, citric acid, and flavoring. Patients were given a 1-gram measuring spoon and were advised to mix a full spoonful of tea directly into either warm or cold water before consuming. They were asked to ingest six such doses per day. Each dose contained 100 calories and 46 mg of caffeine. Treatment was to commence within seven days of trial registration.

Patients met with their oncologists for a history, physical examination, and serum PSA measurement every month. The protocol allowed for follow-up testing every other month in patients who appeared stable over a 6-month period. For patients with radiographic evidence of disease, the protocol required repeat scanning in 4 months but otherwise specified that repeat radiographs were to be left to the discretion of the treating oncologist. Tumor assessment with serum PSA and radiographic testing occurred after 4 months of treatment. An objective tumor response in patients with only PSA elevation was defined as a decline $\geq$ 50% decline in the PSA level on 2 consecutive evaluations at least 4 weeks apart. In patients who also had physical examination or radiographic evidence of disease, standard National Cancer Institute RECIST criteria (http://www.nci.nih.gov/bip/RECIST.htm) were used to assess tumor response as well. Patients who were removed from the trial prior to the 4-month evaluation period were considered to have disease progression. At each monthly visit, patients completed a questionnaire to describe their average daily dosing of green tea.

Toxicity was assessed monthly with the Common Toxicity Criteria (CTC) from the National Cancer Institute (version 2). No dose modifications were included in the protocol, but patients were withdrawn for Grade 3 or 4 treatment-related toxicity.

Endpoints and Statistics

The primary endpoint of this trial was the estimated percentage of patients with prostate carcinoma who sustained a decline in PSA level with green tea. We expected to observe such a decline in 5% of patients by coincidence alone. A two-stage, Simon Phase II study design was used. A total of 40 patients would allow for a Type I error rate of 5% and 90% power to detect a true response probability of 20%. A confidence interval for the true response rate was calculated according to the approach of Duffy and Santner.[10] Basic descriptive statistics and related graphic representations were used for demographic variables and supportive analyses.

TABLE 1
Baseline Characteristics of 42 Eligible Patients

Characteristic	No. of patients (%)
Age (yrs)[a]	75 ± 9
Eastern Cooperative Oncology Group (ECOG) Performance Status	
0	27 (64)
1	13 (31)
2	2 (5)
PSA (ng/dL)[a]	583 ± 2165
Evaluation of metastatic disease	
PSA elevation only	35 (83)
PSA elevation and radiographic physical examination	7 (17)
Prior treatment	
Prostatectomy	17 (40)
Radiation	23 (55)
Chemotherapy	14 (33)
Other	12 (29)

ECOG: Eastern Cooperative Oncology Group; PSA: prostate specific antigen.
[a] Mean ± standard deviation.

RESULTS

Patient Characteristics

A total of 54 patients were enrolled. Three patients choose to withdraw from the study before receiving any study drug. Nine other patients were deemed ineligible after enrollment on retrospective review of study records for the following reasons: 1) two patients had continued on hormone therapy for too long prior to enrollment and, thus, did not meet the eligibility criteria; 2) one patient was symptomatic with metastatic disease at the time of enrollment and, thus, did not meet the eligibility criteria; and 3) six patients had not had serial PSA levels drawn prior to enrollment and, thus, did not meet the eligibility criteria for PSA elevation, as defined by the Prostate Specific Antigen Working Group and by the protocol. Therefore, 42 patients were considered eligible and evaluable (Table 1). Because six ineligible patients had not had serial PSA levels drawn prior to enrollment, we also report a supplemental analysis that included these patients.

Response

Among the 42 eligible patients, 1 patient manifested a 50% decrease in PSA level from baseline. This patient's

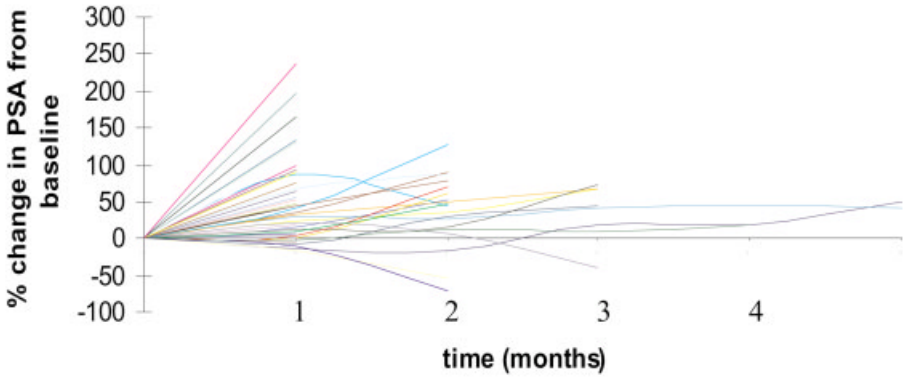

FIGURE 1. Only 1 patient within this 42-patient cohort manifested a 50% decline in prostate specific antigen (PSA) values from baseline.

TABLE 2
Reasons for Patient Drop Out

Reason for drop out	Proportion of patients (%)
Declined further green tea	25
Experienced an adverse event	3
Demonstrated disease progression	63
Other medical problems precluded participation	9

PSA level dropped from 229 ng/dL to 105 ng/dL. This decrease was not sustained beyond 2 months. This observation resulted in an estimated response rate of 2% (95% confidence interval, 1–14%) and was below what was expected to occur by chance alone. Based on only physical examination and radiographic assessment, there were no nonbiochemical tumor responses. Including the six ineligible patients in a post hoc supplemental analysis did not change the results significantly, although another response was detected. At the end of the first month, the median change in PSA level from baseline for the cohort increased by 43% (Fig. 1).

Time on Study and Compliance

The median time on study was 1 month. The most common reason for dropping out prior to the 4-month assessment was disease progression, and it is unknown whether the decision to drop out was initiated by the treating oncologist or the patient. The second most common reason for dropping out was the patient declining further treatment, presumably because of toxicity (Table 2). While patients were on the study, however, they reported good compliance. During the first 5 months of treatment, patients consistently reported consuming on average between 5 and 6 doses per day.

Toxicity

The majority of patients within the entire cohort (n = 51 patients) tolerated the green tea relatively well. Thirty-one percent of patients reported no toxicity whatsoever directly attributable to the green tea. When toxicity did occur, it usually was Grade 1 or 2 and included nausea, emesis, insomnia, fatigue, diarrhea, abdominal pain, and confusion. However, six Grade 3 events occurred, and one Grade 4 event also occurred. The six episodes of Grade 3 toxicity involved insomnia, confusion, diarrhea, fatigue, and abdominal pain. The one episode of Grade 4 toxicity involved confusion, and the patient recovered after a 5-day hospitalization.

DISCUSSION

This trial explored the antineoplastic effects of green tea in asymptomatic patients with androgen independent prostate carcinoma. Green tea demonstrated limited activity in this setting. Only one patient manifested a decline in serum PSA, and no patient manifested a tumor response on radiographic assessment or physical examination. Thus, at best, our response rate was 2% (95% confidence interval, 1–14%). This response rate was below the hypothesized level of 5% attributable to mere chance. Based on these results, we conclude that green tea, as administered in this trial, does not merit further investigation in the treatment of patients with androgen independent prostate carcinoma.

The current findings are important, because large numbers of patients with malignant disease resort to green tea. The use of so-called *alternative* medicine has increased over the past 10 years, and the use of herbal preparations, such as green tea, also has increased.[1,2] Such trends suggest that patients with prostate carcinoma may well be drinking green tea in

the hope of gleaning antitumor effects. Our findings suggest that these patients' time and effort may be spent better exploring other therapeutic strategies. Moreover, although green tea was tolerated well for the most part, a notable percentage of patients did experience toxicity, presumably from the tea's caffeine. The fact that there were six episodes of Grade 3 toxicity and one episode of Grade 4 toxicity suggests that even green tea may result in notable toxicity when it is administered in high doses, possibly inviting caution from patients who participate in *alternative* medicine and from oncologists who provide their medical care.

Can we claim with certainty that green tea holds no antitumor activity whatsoever in patients with prostate carcinoma? It is important to point out that we studied only patients with androgen independent prostate carcinoma. It is possible that green tea may exert antineoplastic effects in patients who have less refractory forms of prostate carcinoma, such as hormone-sensitive prostate carcinoma. In addition, we did not determine whether green tea decreased the risk of disease recurrence among patients with a prior history of prostate carcinoma or among other patients at high risk for developing prostate carcinoma. These acknowledgments may help reconcile the negative findings of the current trial with previously published, large epidemiologic studies, which suggest that green tea confers antitumor effects in relatively healthy populations.

To reconcile our findings with the previous preclinical data on green tea, it is important to point out that many of green tea's alleged antitumor mechanisms of action require prolonged exposure to the agent. For example, inhibition of proteolytic enzymes to prevent metastases, alterations in cell communication, and antiangiogenesis have been touted as explanations for green tea's antineoplastic effects in the laboratory, and many such mechanisms lead to tumor regression only after prolonged exposure to an antineoplastic agent.[11–13] In our trial, the median time on study was only 1 month. Patients or their oncologists interpreted an early rise in PSA as evidence of tumor progression and deemed continued treatment futile, despite the fact that the protocol called for a 4-month treatment period. It may be argued that a longer treatment period and continued treatment, even after an initial rise in PSA, may have lead ultimately to tumor response. Should other investigators choose to study green tea in the future, some consideration may be given to an obligatory, prolonged duration of therapy in patients who remain asymptomatic.

In summary, this preliminary investigation demonstrated a low response rate with green tea among patients with androgen independent prostate carcinoma. Green tea was well tolerated for the most part, but there were six episodes of Grade 3 toxicity and one episode of Grade 4 toxicity that were attributable directly to green tea. Although patients in this trial were not exposed to green tea for a long period, our results suggest that approaches other than green tea should be explored in the treatment of patients with androgen independent prostate carcinoma.

REFERENCES

1. 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;161:1521–1524.
2. Jacobson JS, Chetty AP. Complementary and alternative medicine in prostate cancer. *Curr Oncol Rep.* 2001;3:448–452.
3. Paschka AG, Butler R, Younf CY. Induction of apoptosis in prostate cancer cell lines by the green tea component, (−)-epigallocatechin-3-gallate. *Cancer Lett.* 1998;130:1–7.
4. Gupta S, Hastak K, Ahmad N, et al. Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. *Proc Natl Acad Sci USA.* 2001;98:10350–10355.
5. Imai K, Suga K, Nakachi K. Cancer-preventive effects of drinking green tea among a Japanese population. *Prev Med.* 1997;26:769–775.
6. Jain MG, Hislop GT, Howe GR, et al. Alcohol and other beverage use and prostate cancer risk among Canadian men. *Int J Cancer.* 1998;78:707–711.
7. Heilbrun LK, Nomura A, Stemmermann GN. Black tea consumption and cancer risk: a prospective study. *Br J Cancer.* 1986;54:677–683.
8. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for Phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate Specific Antigen Working Group. *J Clin Oncol.* 1999; 17:3461–3467.
9. Pisters KMW, Newman RA, Coldman B, et al. Phase I trial of oral green tea extract in adult patients with solid tumors. *J Clin Oncol.* 2001;19:1830–1838.
10. Duffy DE, Santner TJ. Confidence intervals for a binomial parameter based on multistage designs. *Biometrics.* 1987;43: 81–93.
11. Jankun J, Selman SH, Swierrcz R, Skrzypczak-Jankun E. Why drinking green tea could prevent cancer. *Nature.* 1997;387: 561.
12. Stoner GD, Mukhtar H. Polyphenols as cancer preventive agents. *J Cell Biochem.* 1995;22:169–180.
13. Lamy S, Gingras D, Beliveau R. Green tea catechins inhibit vascular endothelial growth factor receptor phosphorylation. *Cancer Res.* 2002;62:381–385.