Phase I Trial of Oral Green Tea Extract in Adult Patients With Solid Tumors

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Purpose: **This trial was designed to determine the maximum-tolerated dose, toxicity, and pharmacology of oral green tea extract (GTE) once daily or three times daily.**

Patients and Methods: **Cohorts of three or more adult cancer patients were administered oral GTE with water after meals one or three times daily for 4 weeks, to a maximum of 6 months, depending on disease response and patient tolerance. Pharmacokinetic analyses were encouraged but optional.**

Results: **Dose levels of 0.5 to 5.05 g/m² qd and 1.0 to 2.2 g/m² tid were explored. A total of 49 patients were studied. Patient characteristics: median age, 57 years (range, 27 to 77 years); 23 patients were women (47%); 98% had a Zubrod PS of 1%; 98% had PS of 1; and 21 had non–small-cell lung, 19 had head & neck cancer, three had mesothelioma, and six had other. Mild to moderate toxicities were seen at most dose levels and promptly reversed on discontinuation of GTE. Dose-limiting toxicities were caffeine related and included neurologic and gastrointestinal effects. The maximum-tolerated dose was 4.2 g/m² once daily or 1.0 g/m² three times daily. No major responses occurred; 10 patients with stable disease completed 6 months of GTE. Pharmacokinetic analyses found accumulation of caffeine levels that were dose dependent, whereas epigallocatechin gallate levels did not accumulate nor appear dose related.**

Conclusion: **A dose of 1.0 g/m² tid (equivalent to 7 to 8 Japanese cups [120 mL] of green tea three times daily) is recommended for future studies. The side effects of this preparation of GTE were caffeine related. Oral GTE at the doses studied can be taken safely for at least 6 months.**

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TEA IS A BEVERAGE made from the leaves of *Camellia sinensis* species of the theaceae family. This beverage is one of the most ancient and is, next to water, the most widely consumed liquid in the world. Tea leaves are primarily manufactured as green, black, or oolong, with black tea representing approximately 80% of tea products consumed. Green tea is the nonoxidized, nonfermented product and contains several polyphenolic components, such as epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate (EGCG).

The primary polyphenol in green tea extract (GTE) is EGCG. In 1987, Fujiki et al[1] first reported that EGCG significantly inhibited tumor promotion of teleocidin in a two-stage carcinogenesis experiment on mouse skin. Significant anticarcinogenic effects of EGCG and GTE on various organs, such as skin, stomach, duodenum, colon, liver, pancreas, and lung in rodent models have been confirmed.[2-12] Possible preventive effects of tea consumption on cancer development in humans have been reported. Many studies have found no significant association,[13-18] whereas others have found an increase in cancer risk.[19-21] Other studies found a protective effect of tea consumption against cancer.[22-27] Many of the studies that found no effect or a negative effect of tea consumption were done in Western countries, while a cancer preventive effect was primarily seen in Asian countries, especially China and Japan, where inhabitants drink large amounts of green tea each day. The reason for these differing results may be due to variable consumption of tea, with much larger volumes typically being consumed in Asian countries.[28]

To determine the protective effects of green tea intake against cancer incidence, a prospective cohort study was undertaken to examine whether green tea prevented cancer development in a population that consumed large amounts of green tea.[28] A survey of 8,552 individuals over 40 years of age living in a town in Saitama prefecture in Japan was carried out. During the 9 years of follow-up (71,248.5 person-years), 384 cases of cancer were identified. A negative association between green tea consumption and cancer incidence, especially among females drinking more than 10 cups (cup = 120 mL) a day was found. A slowdown in increase of cancer incidence with age was observed among females who consumed more than 10 cups a day; consumption of green tea was associated with later onset of

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cancer. Age-standardized average annual incidence rate was significantly lower among females who consumed large amounts of green tea. Relative risk of cancer incidence was also lower among both females (RR = 0.57; 95% confidence interval [CI], 0.33 to 0.98) and males (RR = 0.68; 95% CI, 0.39 to 1.21) in groups with the highest consumption, although the preventive effects did not achieve statistical significance among males, even when stratified by smoking and adjusted for alcohol and dietary variables.[28]

These epidemiologic findings have spurred intense basic science research of green tea and its components. These studies have suggested several possible mechanisms of action of green tea. Antioxidant properties[29] or interactions with certain enzymes or proteins implicated in cancer biology such as urokinase,[30] ornithine decarboxylase,[31] NADPH-cytochrome P450 reductase,[32] protein kinase C,[33] steroid 5 alpha reductase,[34] TNF expression,[35] and nitric oxide synthase[36] have been proposed as possible mechanisms of action. More recently, an anticancer effect through antiangiogenesis activity of green tea and EGCG has been reported by Cao et al.[37] Naasani et al[38] have demonstrated that EGCG strongly and directly inhibits telomerase, an enzyme essential for unlocking the proliferative capacity of cancer cells by maintaining the tips of their chromosomes. Green tea may protect against cancer by causing cell cycle arrest and inducing apoptosis.[39] Investigators in Italy recently published evidence that green tea may exert its beneficial effect by impairing tumor invasion and nourishment through direct inhibition of two gelatinases (MMP-2 and MMP-9).[40] Despite these tantalizing reports, the exact mechanism underlying the anticancer effect of green tea remains elusive.

A study of oral GTE conducted in healthy Japanese volunteers found that the administration of 2.25 g of GTE given as three divided doses was safe. This was equivalent to approximately 10 cups (120 mL each) of green tea daily. We conducted this phase I trial, which is the first trial conducted in the world of oral GTE in cancer patients. The objectives of this trial were to determine the maximally tolerated dose (MTD) of oral GTE on a once daily and three times daily schedule in adult cancer patients. The safety and side effects of chronic daily GTE, clinical pharmacology of GTE, and antitumor activity of GTE were determined. Given the safe administration of 2.25 g of GTE (divided into three equal doses) proven in the volunteer study above, the first dose level of this study was 0.5 g/m^2, once daily.

PATIENTS AND METHODS

Forty-nine patients with histologic or cytologic proof of incurable malignancy who were either refractory to standard therapy or had a disease for which no standard therapy existed were entered between August 1997 and April 1999. Eligibility requirements included an estimated life expectancy of at least 16 weeks, a Zubrod performance status of zero or one, and age of 18 to 80. Patients could not have received chemotherapy or radiotherapy for 3 weeks before study entry (6 weeks for mitomycin or nitrosourea). Baseline laboratory parameters included a WBC count of more than 4,000/mL,[3] platelet count of more than 100,000/mL,[3] bilirubin of less than or equal to 1.5 mg/dL, ALT or AST of less than 1.25× normal, and creatinine levels of less than or equal to 1.5 mg/dL. Patients could not have a history of significant cardiac disease, metabolic disorder, infection, or brain metastases. Written informed consent was obtained from all patients. All patients were requested to participate in the pharmacokinetic studies, but participation in this was not mandatory. This study was reviewed and approved by the institutional review board of the University of Texas M. D. Anderson Cancer Center.

Table 1. Composition of Green Tea Extract Capsules in This Study

Strength of capsule, mg	110
	200
	270
Composition of green tea extract, %	
Catechins, total	26.9
EGCg	13.2
EGC	8.3
ECg	3.3
EC	2.2
Caffeine	6.8
Protein	19.8
Lipid	0.1
Amino acids	4.5
Ash	10.8
Moisture	2.6
Other (carbohydrate, flavonoid, etc)	28.5

Before therapy, all patients had a complete history and physical examination. Pretreatment laboratory evaluation parameters included an electrocardiogram reading, complete blood count, platelet count, urinalysis, sodium, potassium chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium protein, albumin, phosphorus, uric acid, alanine serum transferase, bilirubin, lactate dehydrogenase, alkaline phosphatase, cholesterol, triglyceride, prothrombin time, and partial thromboplastin time. During the first 4 weeks of the study, patients had a complete blood count, platelet count, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, and creatinine assessment repeated weekly. Every 4 weeks, an interim history, physical, and pill count were performed, as well as the pretreatment laboratory examinations. Radiologic examinations to document tumor measurements and response were performed every 4 weeks. Standard criteria for response and the common toxicity criteria of the National Cancer Institute (NCI; version 2.0, NCI common toxicity criteria, CTEP) were used.

Green tea extract was supplied in capsule form by Ito En, Ltd. (Tokyo, Japan). The capsules came in three different strengths: 110, 200, and 270 mg. Composition of the capsules is listed in Table 1. Patients were instructed to take the GTE capsules as a once-daily dose (initial seven cohorts) or as a three-times-a-day dose (final three cohorts). Capsules were to be taken after meals with water. At least three patients were entered at each dose level; additional patients were added at levels at which toxicity was observed. Responding- or stable-disease patients were allowed to continue on study for a

maximum of 6 months. The initial dose level was 0.5 g/m^2, and dose escalation proceeded at 100% until grade I toxicity was observed. Dose escalation then continued at 50% until grade II toxicity occurred and thereafter, at 25% increments until the MTD was defined. Dose escalation was not permitted in the same patient. Dose escalation proceeded from 1.0 g/m^2 to 5.05 g/m^2. Once the MTD was determined for a once-daily schedule, the study was amended to explore a three-times-daily dosing schedule. The initial level evaluated was 1.7 g/m^2 tid. Dose escalation to 2.2 g/m2 tid found that long-term use of the GTE was not possible secondary to the side effects observed. The dose was then reduced to 1.36 and 1.0 g/m^{2,} each given on a tid schedule, as toxicities were encountered. This dose de-escalation was performed to define the dose that was most likely to be tolerated on a long-term basis. Pharmacokinetic studies were done in as many patients as possible at each dose level. The MTD was defined as that dose that produced reversible toxicity (≥2+ magnitude) in 70% of the patients or at least 3+ toxicity in 30% of patients.

Pharmacokinetic Studies

Pharmacokinetic studies were performed on day 1 and again in the same manner at the end of weeks 4 and 8. Ten-milliliter blood samples were obtained before treatment and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 24 hours after drug ingestion for patients taking GTE on a once-daily basis. For patients entered on the three-times-daily schedule, a 10-mL blood sample was obtained before the each dose of drug and was also obtained 2 hours after the initial and second dose on day 1 and at the end of weeks 4 and 8. On the days of study, the GTE was taken at least 4 hours apart, beginning at 8 AM. Urine samples were collected only for patients on the once-daily schedule.

Analytic Methodology

Caffeine. Caffeine was determined using a validated high-performance liquid chromatography (HPLC) assay. Plasma samples were extracted using Waters Oasis HLB cartridges (Waters Associates, Milford, MA). Aliquots (200 μL) of sample plasma were loaded onto prepared cartridges that were then washed with water (1 mL). Caffeine was eluted using 1 mL MeOH that was then dried under nitrogen. Samples were reconstituted with MeOH (100 μL), and an aliquot of this solution injected onto the HPLC. Analyses of caffeine was performed using a Spherisorb ODS analytic HPLC column (Phenomenex, Torrence, CA). The isocratic mobile phase consisted of 0.5% acetic acid and acetonitrile (80:20; v:v) and was run at a flow rate of 1 mL/min. Caffeine was detected at 276 nm. The HPLC instrument was a Waters Alliance model 2,690. Authentic caffeine was purchased from Sigma Chemical Co. (St. Louis, MO).

Unconjugated (free) catechin assay. Catechin standards (EGCg, ECg, EGC, and EC) were obtained from Ito En, Ltd. Spiked plasma samples and patient samples (500 μL) were extracted using a modification of the method reported by Poon.[41] An aliquot of internal standard (ethyl gallate) was added to samples in a microcentrifuge tube. Proteins were precipitated by adding cold acetonitrile (500 μL). Samples were then processed by centrifuge (23,000 × *g*) for 5 minutes at 5 EC. The supernatant was transferred to a new tube to which was added 100 μL 1M ammonium acetate and ethyl acetate (750 μL). Samples were vortex mixed for 20 minutes and then processed by centrifuge (23,000 × *g*) for 3 minutes. The upper organic layer of each sample was transferred to a clean glass tube. A second extraction of the sample using 750 μL ethyl acetate was conducted and the extract supernatant solutions combined. These were then dried under nitrogen at 40 EC. The dried samples were reconstituted with 100 μL 10:90 acetonitrile:0.1% formic acid (pH 3.0) and mixed. The clear supernatant was then transferred to a sample vial for analysis by liquid chromatography (LC)/mass spectometry (MS).

Prepared sample extracts were analyzed using a validated LC/MS method. Reconstituted samples (50 μL) were injected into a MicroMass (Beverly, MA) VG platform mass spectrometer equipped with an electrospray inlet source using a Hewlett Packard 1,100 HPLC apparatus equipped with a photodiode array detector. Catechins were separated using an isocratic method with a total run time of 7 minutes. The mobile phase consisted of acetonitrile: 0.1% formic acid (pH 3.0; 20:80, v:v) and was run at 300 μL/min. The column used was a YMC-basic *S*-5 column (2.0 × 250 nm; YMC, Inc., Waters Corp., Milford, MA). Catechins were detected using selective ion monitoring (EGCg, *m/z* 457; EGC, *m/z* 441; ECg, *m/z* 305; EC, *m/z* 289; ethyl gallate, *m/z* 197) with the mass spectrometer operated in an electrospray-negative mode.

Table 2. Patient Characteristics (N = 49)

Sex		
Male		26
Female		23
Age, years		
Median		57
Range		27-77
Zubrod performance status		
1		48
2		1
Prior treatment		
Chemotherapy		39
Radiation		37
Surgery		38
None		3
Diagnosis		
Non–small-cell lung cancer, total		21
Head and neck cancer, total	19	
Squamous	10	
Adenoid cystic	5	
Other salivary gland	3	
Lymphoepithelioma	1	
Mesothelioma	3	
Thymoma	2	
Other	4	

RESULTS

Forty-nine adult cancer patients were entered onto this phase I trial between August 1997 and April 1999. Patient characteristics are listed in Table 2. Twenty-six (53%) were male, and the median age was 57 years. All patients had an excellent performance status. As is typical for a phase I population, the vast majority of patients had received prior anticancer therapy. Non–small-cell lung cancer accounted for the most common type of malignancy (21 patients, or 43%). Cancer of the head and neck comprised the second most common type of cancer diagnosis, and there were a

Table 3. Number of Green Tea Extract Capsules and Total Daily Dose

Dose (g/m^2)	No. of Patients	No. of Capsules/ Dose	Total GTE Dose (gm)
Once daily			
0.5	3	4-10	0.8-1.1
1.0	3	6-11	1.5-2.2
1.5	3	10-20	2.3-2.6
2.25	3	18-19	3.2-4.9
3.37	6	21-32	5.5-6.4
4.2	6*	28-46	6.1-9.9
5.05	3*	31-39	8.2-10.1
Three times daily			
1.0	8†	7-10	4.8-6.7
1.36	7‡	9-20	6.6-8.9
1.7	4	12-15	8.9-11.4
2.2	3	14-18	9.9-13.6

*One patient stopped after one dose.

†One patient refused therapy after registration.

‡One patient removed from study after 3 days for unrelated medical problem.

few patients with mesothelioma, thymoma, or other diagnosis.

The dose levels, number of patients entered at each level, number of capsules consumed per dose, and the total daily dose of GTE taken are listed in Table 3. Because of the strength of the capsules available for use in this study (110, 200, and 270 mg), many patients consumed a large quantity of capsules per dose. This is outlined in greater detail in Table 3; however, the range of capsules per dose was 4 (0.5 g/m^2 daily) to 46 (4.2 g/m^2 daily). Four patients were not evaluable for toxicity or response. Two of these patients refused further study medication after one dose (one each at 4.2 and 5.05 g/m^2 daily), one patient declined to participate in the study after registration, and one patient was removed from study after 3 days for an unrelated comorbid illness (perforated diverticulum).

Toxicity data is presented in Table 4. None of the patients developed hematologic toxicity as a consequence of GTE consumption. During the trial, two patients had a grade 1 increase in serum cholesterol, and four patients had a grade 1 increase in serum triglyceride. No trends were noted, and it was the opinion of the investigators that the minor differences in cholesterol and triglyceride values most likely reflected temporary changes in diet than any real effect of GTE. In addition, follow-up laboratory examinations found no significant changes in serum chemistries, coagulation, electrocardiographs, or urinalysis.

No toxicities were seen in the three patients treated at the initial dose level of 0.5 g/m^2 daily. Grade 1 toxicities were seen at dose levels 1.0, 1.5 and 2.25 g/m^2. These toxicities were mild and included gastrointestinal (abdominal bloating, sore throat, and nausea), neurologic (insomnia, paresthesias, restlessness), and cardiovascular (palpitations) complaints. Two patients (one each at the 1.0 and 1.5 g/m^2 levels) complained of polydipsia and urinary frequency. The cohort treated at 3.37 g/m^2 was expanded to six patients after grade 2 toxicity was observed. At this dose level, similar toxicities to that seen in the previous three dose levels were observed, with gastrointestinal, neurologic, and cardiovascular toxicities observed. In addition, the constitutional complaints of diaphoresis and fatigue were seen. Because only one of six patients experienced grade 2 toxicity, dose escalation to 4.2 g/m^2 proceeded. There was no notable increase in toxicity seen at this level. One of six patients experienced grade 2 toxicity (fatigue and nausea) and declined further treatment after only one dose. At 5.05 g/m^2 daily, three patients were studied. The first patient had only grade 1 toxicity. The second patient initially took the prescribed GTE incorrectly on a divided-dose, three-times-daily schedule with no toxicity. When this error was corrected to a once-daily schedule, the same patient developed grade 1 diaphoresis, dyspepsia, and insomnia; grade 2 cough; constipation; headache and pain; and grade 3 tremors. The third patient entered at this level withdrew from the study after the initial dose, which had caused the patient to have grade 2 abdominal bloating and nausea.

On the basis of the toxicity seen at the 5.05 g/m^2 daily level, the protocol was amended to explore a tid schedule. The initial dose on the tid schedule was 1.7 g/m^2 three times daily (total daily dose of 5.1 g/m^2). Four patients were entered at this level (one additional patient was entered at this level through a registration error). One patient experiencing no toxicity, two patients with grade 1 toxicity and one patient with grade 2 abdominal bloating, nausea, and emesis. Dose escalation to 2.2 g/m^2 tid (total daily dose of 6.6 g/m^2) found similar toxicities to those reported previously with gastrointestinal complaints (abdominal bloating, flatulence, nausea and vomiting) being most common. Given the degree of symptoms that patients were experiencing, a dose de-escalation to further define a more tolerable dose for long-term use was undertaken. The third cohort of patients treated on the tid schedule received 1.36 g/m^2 (4.08 g/m^2 total daily dose) of GTE. The cohort was expanded to six patients after the third patient at this level experienced grade 2 fatigue and palpitations and grade 3 constipation. A additional 4 patients were registered to this level (one patient was not evaluable for toxicity after coming off study—ruptured diverticulum—after 3 days of GTE). The toxicities observed are noted in Table 4 and were similar to those previously seen. The final dose level was 1.0 g/m^2 tid (total daily dose of 3.0 gm/2). After the initial three patients entered had minor toxicities, the dose level was

Table 4. Toxicity of Oral Green Tea Extract

Side Effect	NCI Grade	Dose Level, mg/m^2										
		Once Daily							Three Times Daily			
		0.5 (n = 3)	1.0 (n = 3)	1.5 (n = 3)	2.25 (n = 3)	3.37 (n = 6)	4.2 (n = 6)	5.05 (n = 3)	1.0 (n = 8)	1.36 (n = 7)	1.7 (n = 4)	2.2 (n = 3)
Cardiovascular												
Hypertension	1	0	0	0	0	1	0	0	0	0	0	0
Palpitations	1	0	0	0	1	1	0	0	0	1	0	0
	2	0	0	0	0	0	0	0	0	1	0	0
Constitutional												
Diaphoresis	1	0	0	0	0	0	0	1	0	1	0	0
	2	0	0	0	0	1	0	0	0	0	0	0
Fatigue	1	0	0	0	0	2	0	0	0	1	0	0
	2	0	0	0	0	1	1	0	1	2	0	0
Gastrointestinal												
Abd bloating	1	0	0	1	1	1	0	1	0	1	2	2
	2	0	0	0	0	1	0	1	0	0	0	0
Anorexia	1	0	0	0	0	0	0	0	0	1	0	0
Constipation	1	0	0	0	0	0	0	0	0	2	0	0
	2	0	0	0	0	0	0	1	0	0	0	0
	3	0	0	0	0	0	0	0	0	1	0	0
Diarrhea	1	0	0	0	0	0	0	1	0	1	0	0
Dyspepsia	1	0	0	0	0	1	0	1	0	1	0	0
Dysphagia	1	0	0	0	0	0	0	0	0	0	0	1
Flatulence	1	0	0	0	0	2	0	0	1	2	0	2
	2	0	0	0	0	0	0	0	0	1	0	0
Nausea	1	0	1	3	1	2	3	1	1	3	2	0
	2	0	0	0	0	1	1	1	0	1	1	1
Odynophagia	1	0	0	1	1	0	0	0	0	0	0	0
Polyphagia	1	0	0	0	0	0	1	1	1	0	0	1
Vomiting	1	0	0	0	0	0	1	1	0	1	1	1
	2	0	0	0	0	1	0	0	0	1	1	1
Neurologic												
Agitation	1	0	0	0	0	0	0	0	2	1	0	0
Dizziness	1	0	0	0	0	0	1	0	0	1	0	0
Insomnia	1	0	0	1	0	2	0	0	3	2	0	0
Memory	1	0	0	0	0	0	0	2	0	1	0	0
Paresthesia	1	0	0	1	0	0	0	0	0	0	0	0
Restlessness	1	0	2	1	1	0	1	1	0	1	1	0
Tremor	1	0	0	0	0	1	0	3	0	0	0	0
	3	0	0	0	0	0	0	0	0	0	0	0
Pain												
Headache	1	0	0	0	0	0	1	0	1	1	0	0
	2	0	0	0	0	0	0	1	0	0	0	0
Pain	1	0	1	0	0	0	0	0	0	0	0	1
	2	0	0	0	0	0	0	1	0	0	0	0
Renal												
Dysuria	1	0	0	0	0	0	0	0	0	0	0	1
Polyuria	1	0	1	1	0	0	0	1	0	0	0	0
Other												
Cough	2	0	0	0	0	0	0	1	0	0	0	0
Myalgia	1	0	0	0	0	0	0	0	0	1	0	0
Polydipsia	1	0	1	1	0	0	0	0	0	0	0	1

expanded, enrolling a total of eight patients. One patient did not participate in the study after registration and did not take any GTE. Of the seven patients who did complete at least 1 month of GTE, three patients did not experience any toxicity. The other four patients had grade 1 toxicity consisting of insomnia,[3] agitation,[2] fatigue,[2] or mild gastrointestinal complaints. On the basis of the tolerable nature of the side effects seen at the 1.0 g/m^2 level, the trial was concluded.

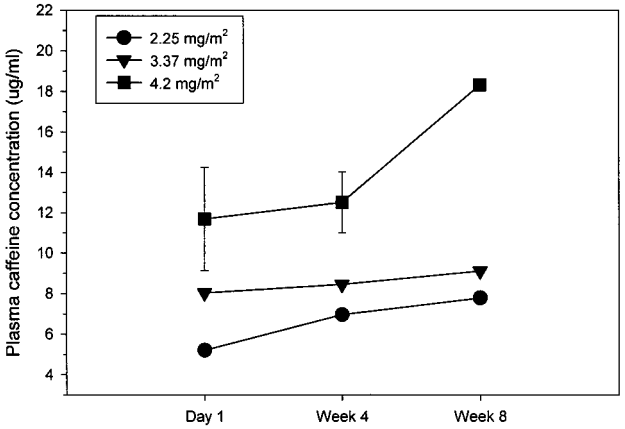

Fig 1. Dose-dependent increases in plasma caffeine concentrations as a function of duration of therapy with green tea extract (GTE). Data are presented as mean caffeine Cmax concentrations after the daily dose of GTE on day 1, as well as the initial day of therapy on weeks 4 and 8. In the highest dose group, data are presented as mean ± SD.

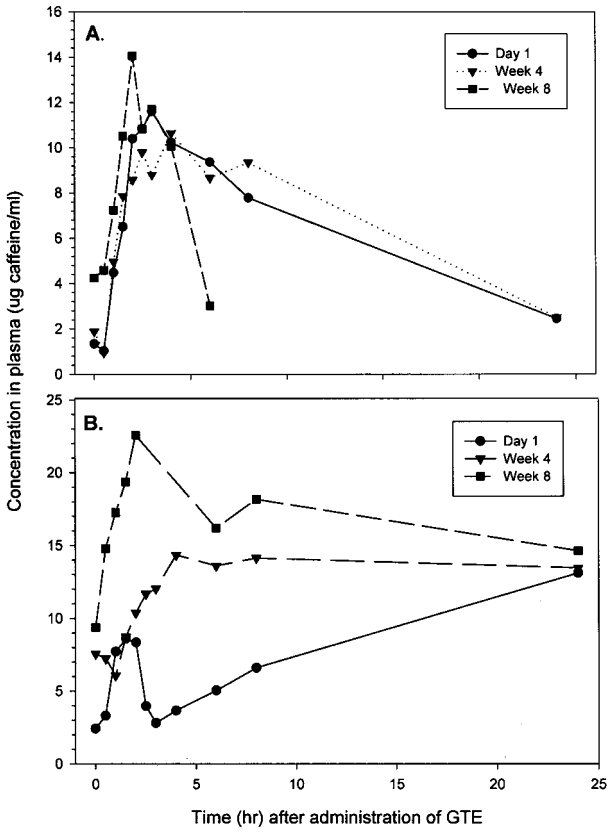

Fig 2. Individual variation in caffeine pharmacokinetics. Data show plasma caffeine concentrations versus time plots after administration of green tea extract (GTE) at 4.2 mg/m^2 to two separate patients. (A) This patient showed reproducible caffeine pharmacokinetics throughout the 8-week trial of GTE. (B) This patient showed clear evidence of time-dependent accumulation of plasma caffeine concentrations; these data were indicative of approximately 33% of all patients entered at this dose level.

No major or minor antitumor responses were seen during the trial. The median duration of therapy was 2 months. Two patients refused further participation in the study after one dose. One patient came off study after 3 days when he developed a perforated diverticulum that was judged unrelated to therapy. Fifteen patients completed 1 month, 16 patients completed 2 months, 3 completed 3 months, one took 4 months of treatment, and 10 patients with stable disease completed the full possible 6 months of oral GTE.

Pharmacokinetic Results

Caffeine. As shown in Fig 1, plasma caffeine Cmax concentrations were dose-dependent on the once-daily schedule, and average concentrations ranged from 5 μg/mL at 2.25 g/m^2 to 11.4 μg/mL at 4.2 g/m^2. Within dose levels, plasma caffeine concentrations were observed to increase over the 8-week investigation period. As seen in Fig 2, however, there was considerable variation between patients with respect to relative caffeine pharmacology. For example, there was no detectable increase in caffeine Cmax or clearance throughout the duration of the study for the patient in Fig 2A. In contrast, the patient data in Fig 2B show a clear time-dependent accumulation of caffeine with Cmax levels reaching 23 μg/mL by week 8. On the tid schedule at 1.0 g/m^2, the dose recommended for phase II trials, plasma caffeine levels also exhibited considerable interpatient variability and ranged from 1.5 to 5 μg/mL throughout the daily doses.

Catechins. Catechins exist in plasma as either free compounds or in several conjugated forms.[42] Because only free catechins are believed to possess an antioxidant activity,[43] no attempt was made to hydrolyze conjugated catechins to provide a measure of total catechin content. The method employed in the present study routinely permitted quantitation of both EGCG and ECG in patient plasma samples. Plasma levels of ECG and EC were low and variable. The dose-response relationship of GTE to plasma EGCG concentration is shown in Fig 3. In contrast to caffeine, there was no indication of any time-dependent accumulation of catechin over the 8-week period of study. Although numbers of data sets per dose level were small, determination of EGCG in plasma revealed a Tmax of 1 to 3 hours and Cmax levels of 100 to 225 ng/mL. No EGCG was detected in the urine. Analyses of plasma from patients on the tid schedule revealed EGCG concentrations of 35 to 55 ng/mL with no accumulation of catechin over the 8-week period of the study.

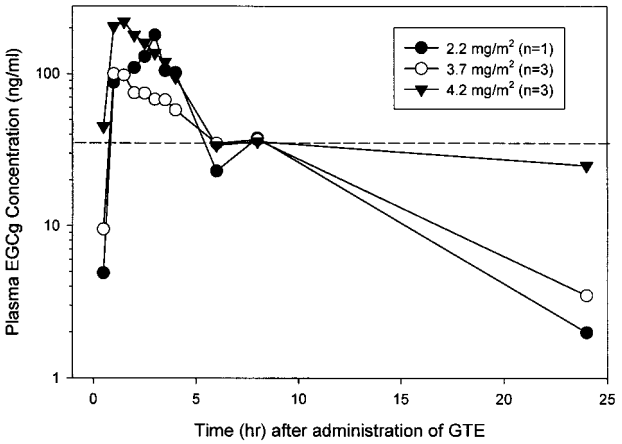

Fig 3. Dose-related plasma epigallocatechin gallate (EGCG) concentrations as a function of time after administration of green tea extract (GTE). EGCG pharmacokinetics were similar at all dose levels. Numbers in parentheses indicate the number of patient data sets at each dose level. EGCG plasma concentration-time data in patients administered GTE at 1 mg/m² on a tid schedule were greatly reduced from levels reached in the daily single-dose regimen (data not shown).

DISCUSSION

This phase I study of oral GTE was performed after epidemiologic studies suggested a protective effect of tea consumption and preclinical laboratory studies of green tea constituents demonstrated anticancer activity.

This phase I study of oral GTE in adult cancer patients found dose-limiting side effects of gastrointestinal complaints (abdominal bloating, dyspepsia, flatulence, nausea, and vomiting) and CNS stimulation (agitation, dizziness, insomnia, tremors, and restlessness). These side effects were likely related to the 7% caffeine content of the GTE employed in this study. Patients treated at the 1.0 g/m^2 three-times-daily level had tolerable side effects. This dose could likely be administered on a long-term basis, as would be utilized in a chemopreventive setting. This dose of GTE is roughly equivalent to drinking seven to eight Japanese-style cups of green tea three times daily. A decaffeinated product might be better tolerated. This study was done with a caffeinated product because the epidemiologic data in support of this trial[28] was based on consumption of caffeinated green tea. Because drinking 20 to 25 cups of green tea on a daily basis is impractical and, some would say, unpleasant,[44] the development of a capsular alternative of green tea may prove beneficial. The MTD of oral GTE once daily was 4.2 g/m^2. This dose is not recommended for further study because it was not as well tolerated as the divided schedule.

The toxicities observed in this trial appear to be related to relative plasma caffeine levels. Hence, one might consider the possibility of using a decaffeinated GTE product. However, caffeine has been implicated as an important component of the chemoprevention activity of tea. For example, Chung et al[45] have shown that in addition to the polyphenolic compounds in tea, caffeine seems to contribute significantly to its inhibitory activity against lung carcinogenesis in rats. A more recent study[46] has directly compared oral administration of tea, decaffeinated tea, and caffeine itself on the formation and growth of tumors in mice previously treated with ultraviolet B light. The decaffeinated teas were inactive or less-effective inhibitors of tumor formation than the regular teas; adding caffeine back to the decaffeinated teas restored biologic activity. Interestingly, as in the prior study, caffeine alone in the drinking water inhibited the formation of nonmalignant and malignant tumors.

Plasma concentrations of free (unconjugated) catechins were determined in this study. On the single daily-dose schedule, levels of EGCG reached 225 ng/mL after administration of 4.2 g/m^2. This can be compared with total (free plus conjugated) EGCG plasma levels in human volunteers of 326 ng/mL after administration of decaffeinated GTE 4.5 g/m^2 orally.[47] On the 1.0 g/m^2 tid schedule, plasma EGCG levels were, as expected, approximately one third of those observed in patients on the single daily-dose regimen.

The recommended dose for future trials of GTE is 1.0 g/m^2 three times daily. A three-times-daily dosing schedule is recommended over a daily dose because this was better tolerated and allowed administration of more GTE. The side effects of this preparation of GTE were related to caffeine. Oral GTE can be safely taken for at least 6 months. Future trials exploring the use of GTE in patients with oral leukoplakia are planned. These studies will incorporate translational research with biomarker studies. At this point, it would seem that GTE may have more potential as a chemopreventive agent rather than a cytotoxic one.

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