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ORIGINAL ARTICLE

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Phase I study of green tea extract in patients with advanced lung cancer

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Abstract *Purpose*: Epidemiologic studies suggest that consumption of green tea may have a protective effect against the development of several cancers. Preclinical studies of green tea and its polyphenolic components have demonstrated antimutagenic and anticarcinogenic activity, and inhibition of growth of tumor cell lines and animal tumor models, including lung cancer. Green tea may also have chemopreventive properties, and enhancement of cytotoxicity of chemotherapeutic agents has been demonstrated. This trial was designed to determine the maximum tolerated dose (MTD) of green tea extract (GTE) in patients with advanced lung cancer. *Methods*: A total of 17 patients with advanced lung cancer were registered to receive once-daily oral dosing of GTE at a starting dose of 0.5 g/m^2 per day, with an accelerated dose-escalation scheme. *Results*: On this schedule, the MTD of GTE was 3 g/m^2 per day, and at this dose, GTE was well tolerated with no grade 3 or 4 toxicity seen. Dose-limiting toxicities were diarrhea, nausea and hypertension. No objective responses were seen in this trial. Seven patients had stable disease ranging from 4 to 16 weeks; no patient remained on therapy longer than 16 weeks due to the development of progressive disease. *Conclusions*: This study suggests that while relatively nontoxic at a dose of 3 g/m^2 per day, GTE likely has limited activity as a cytotoxic agent, and further study of GTE as a single-agent in established malignancies may not be warranted. Further studies should focus on the potential chemopreventive and chemotherapy-enhancing properties of GTE.

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Abbreviations GTE: Green tea extract · EGCG: Epigallocatechin gallate · EGC: Epigallocatechin · ECG: Epicatechin-3-gallate · EC: Epicatechin · DLT: Dose-limiting toxicity · MTD: Maximum tolerated dose · NSCLC: Non-small cell lung cancer · MDACC: M.D. Anderson Cancer Center

Introduction

After water, tea is the most widely consumed beverage in the world. It is made from the leaves of *Camellia sinensis* species of the Theaceae family. Green tea is the nonoxidized, nonfermented product, and accounts for approximately 20% of world consumption. Although there is conflicting evidence, some epidemiologic studies suggest a cancer-preventive effect associated with the consumption of green tea [4, 6, 12, 20].

In a prospective cohort study performed in Japan, 8500 people were enrolled and followed for 9 years [5]. It was found that those with the highest green tea intake (more than ten cups per day) had a significantly lower relative risk of cancer than those consuming fewer than three cups per day, even when adjusted for variables such as cigarette smoking and alcohol intake. It was also found that women who consumed more than ten cups per day had a decreased age-adjusted cancer incidence. For heavy consumers, the average age to onset of cancer was delayed, by 3 years for men and almost 9 years for women.

Green tea contains several polyphenolic components known as catechins. Total polyphenols represent approximately 40% of the dry weight of green tea extract (GTE), a higher proportion than found in black or oolong tea. EGCG is the major green tea polyphenol. Preclinical studies have shown GTE and EGCG to have antimutagenic and anticarcinogenic properties.

Repeated topical application of EGCG has been shown to inhibit the development of skin tumors in mouse models [3, 19]. GTE given as the sole source of drinking water to mice inhibited the development of skin tumors induced by exposure to ultraviolet B light [15] and lung adenomas arising following treatment with a nicotine-derived carcinogenic nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [18].

EGCG and GTE inhibit the growth of cancer cell lines [7, 8]. Growth inhibition of established skin tumors in papilloma-bearing CD-1 mice was seen with oral administration of green tea, while intraperitoneal administration of green tea polyphenol fraction or purified EGCG led to growth inhibition and rare tumor regressions compared to control animals given vehicle injections only [17].

A study of GTE administered to 108 healthy Japanese volunteers for 6 months has been performed [13]. A total dose of 2.25 g (approximately 1.3 g/m^2) of crude GTE, roughly the equivalent of ten cups of green tea, was administered daily in three divided doses. Of the 108 participants, the majority took the full dose daily for 6 months. Others interrupted their doses ($n=27$), reduced their dose ($n=8$), or stopped taking GTE altogether ($n=4$). The most common reason for interruption was gastrointestinal upset. Most (78%) did not complain of any adverse effects during the study. Only mild to moderate adverse effects were attributable to the GTE; the most common were epigastric discomfort, heartburn, diarrhea and insomnia. It was felt that these symptoms were at least in part attributable to the caffeine contained in the extract.

Epidemiologic studies and preclinical data suggest that green tea and green tea polyphenols may possess chemopreventive and antiproliferative properties. Further, it appears that GTE is relatively nontoxic. This study was performed to determine the MTD of daily oral GTE, administered for up to 6 months, in adult patients with lung cancer.

Patients and methods

Patient eligibility

Adults with a Karnofsky performance status of ≥70% and a pathologically confirmed, advanced, incurable lung cancer were eligible. At the time of study entry, at least 3 weeks must have elapsed since prior chemotherapy or radiotherapy. Patients were required to have adequate bone marrow (leukocyte count ≥4000 mm^{-3} and platelets ≥100,000 mm^{-3}), hepatic (total bilirubin ≤1.5 mg/dl, aspartate aminotransferase less than 1.25 times the upper limit of normal) and renal (serum creatinine ≤ 1.5 mg/dl) function. Patients with brain metastases, or with clinically significant cardiac disease, were excluded. All patients provided signed informed consent. This trial was reviewed and approved by the Institutional Review Board of the Memorial Sloan-Kettering Cancer Center.

Pretreatment evaluation consisted of a complete history and physical examination with determination of baseline performance status, signs and symptoms. Appropriate radiological examinations were performed to fully define the extent of disease. Baseline laboratory studies included an electrocardiogram, urinalysis, a complete blood count and differential, serum electrolytes, creatinine, blood urea nitrogen, albumin, uric acid, bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, prothrombin time and partial thromboplastin time.

Treatment plan

GTE was provided by Ito En (Tokyo, Japan) as 110- and 270-mg soft gelatin capsules. Doses were rounded to the nearest milligram that could be attained with the capsules. GTE was administered once daily by mouth for 4 weeks. Capsules were to be taken in the morning with water following a meal. GTE was manufactured by extracting green tea leaves with hot water (60°C), followed by sequential steps of evaporation, cooling, clarification by centrifugation, filtration, spray drying and then filling and packing. The composition of green tea extract is as follows: EGCG 13.9%, EGC 7.7%, ECG 3.5%, EC 2.6%, gallocatechin 3.0%, gallocatechin gallate 1.7%, catechin 0.7%, catechin gallate 0.5%, caffeine 6.8%, ash 13.6%, moisture 2.9%, protein (total amino acids) 3.8%, other (protein, lipids, carbohydrates) 39.3%.

Based on the safety of a total daily dose of 2.25 g of a similar formulation of GTE seen in healthy volunteers [13], the starting dose for this study was 0.5 g/m^2. Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0 (Bethesda, Md.). DLT was defined as any grade 3 or 4 toxicity seen during cycle 1 of therapy. An accelerated dose-escalation scheme was used. One patient was enrolled per dose level provided no toxicity of grade 2 or greater was seen. If grade 2 toxicity was seen, an additional two patients were enrolled at that dose level and dose escalation was permitted if no DLT was seen. If one patient experienced DLT, then up to six patients were to be enrolled at that dose. If no further DLT was seen in those six patients, then dose escalation occurred. If two or more episodes of DLT were seen, then the immediately preceding dose level was determined to be the MTD. Doses were to have been escalated in the following manner: if no toxicity was seen at a dose level, then the dose was to be increased by 100%. If a dose level was associated with grade 1 toxicity, the dose was to be escalated by 50%. Once grade 2 toxicity was seen, the dose was to be escalated by 25% until the MTD was reached. However, dose escalation inadvertently occurred more rapidly, as the dose was escalated by 100%, not 50%, throughout

the study when only grade 1 toxicity was observed. Dose escalation in individual patients was not permitted.

Patients were seen weekly during treatment for the first month, and thereafter every 4 weeks. Patients experiencing grade 3 or greater toxicity were to have the study compound withheld until resolution of all toxicity. Dosing for subsequent cycles in that patient was to be at the dose level below that which caused the toxicity. Various laboratory parameters were followed during the study, including serial blood counts, electrolytes, and renal and hepatic function. In patients with measurable disease, tumor measurements were performed by physical examination and/or imaging every 4 weeks. Standard bidimensional criteria for response were used. A *complete response* was defined as the complete disappearance of all clinical evidence of active tumor for a minimum of 4 weeks. A *partial response* was defined as a 50% or greater decrease in the sum of the product of the diameters of measured lesions for 4 weeks, without the simultaneous occurrence of an increase in the size of any lesion or the appearance of a new lesion. *Progressive disease* was declared if there was an increase in the sum of the product of tumor measurements of greater than 25%, or the unequivocal appearance of a new lesion. Patients with tumor measurements not fulfilling any of the above definitions were determined to have *no change*. Completion of a full 4-week course of treatment was required to evaluate response. In the absence of disease progression or unacceptable toxicity, patients could be continued on treatment in additional 1-month blocks, with reevaluation every 4 weeks, for a maximum of 6 months.

Results

Patients

Between May 1998 and February 2000, 17 patients were registered, of whom 16 had a diagnosis of NSCLC and one had small-cell lung cancer. Their characteristics are summarized in Table 1. One patient with NSCLC withdrew consent and was never treated, leaving 16 patients evaluable for toxicity.

Table 1 Patient characteristics

Number entered	17
Number evaluable for toxicity	16
Non-small-cell lung cancer	16
Small-cell lung cancer	1
Age (years)	
Median	63
Range	40–75
Women	8
Karnofsky performance status	
90%	5
80%	5
70%	7
Previous therapy	
Chemotherapy	13
Radiotherapy	9

These 16 patients received a median of one complete cycle of therapy (range less than one to four). Two patients did not complete a full 4-week course of GTE, one because of toxicity and the other because of the development of an intercurrent illness. As they did not complete one full cycle of therapy, these patients were not assessable for response, but were included in the assessment of toxicity.

Dose escalation and toxicity

Table 2 summarizes the number of patients treated at each dose level, and the toxicities seen during cycle 1 of therapy. One patient was enrolled at each of the 0.5, 1 and 2 g/m^2 dose levels without any toxicity of grade 2 or greater. The first patient treated at 4 g/m^2 also had no toxicity of grade 2 or greater, permitting dose escalation. DLT was seen in two of four patients treated at 8 g/m^2. These toxicities were grade 3 diarrhea in one patient and grade 3 nausea in the second. The 4 g/m^2 dose level was then expanded. However, DLT was seen in two of the next four patients enrolled at this level (grade 3 diarrhea and grade 3 hypertension, each in one patient). This required a dose de-escalation by 25%, and four patients were enrolled at 3 g/m^2. One patient at this level withdrew after one dose because of the development of an unrelated intercurrent illness, but three remaining patients completed cycle 1 of therapy without any DLT. Thus 3 g/m^2 was declared the MTD of oral GTE when given once daily.

The DLTs of GTE seen in this study were grade 3 diarrhea, nausea and hypertension. These toxicities were ameliorated by dose reduction. One patient treated at the 8 g/m^2 dose level developed grade 3 nausea and grade 2 vomiting and requested to be removed from the study without a trial of a reduced dose. Other drug-related mild (grade 2 or less) toxicities observed included fatigue, dyspepsia, headache, anxiety and insomnia, with the number and frequency of adverse effects increasing with higher doses. No grade 4 toxicities, and no hematologic toxicities, were observed. In eight patients who received more than 1 cycle of therapy, no cumulative toxicities appeared. There were no deaths on study. All patients other than those described above were withdrawn from study because of progression of disease.

Response

No objective responses were seen. Seven of 14 patients who completed at least 1 cycle had progression of disease when reevaluated at the end of the first cycle, and were removed from study. All other patients had no change. Disease stabilization was seen at all dose levels. Six patients who were tolerating the study medication continued on therapy for more than one cycle. No

Table 2 Common and/or dose-limiting toxicities observed with cycle 1 of therapy. Other infrequent grade 1 toxicities included neuropathy—sensory ($n = 3$), cough ($n = 3$), hemoptysis ($n = 2$), pruritus ($n = 2$). Dose-limiting toxicities are indicated in bold type

Dose level (g/m^2)	Number of patients	Number of patients exhibiting National Cancer Institute Common Toxicity Criteria													
		Nausea		Vomiting		Dyspepsia	Diarrhea		Cardiovascular[a]		Anxiety	Insomnia	Fatigue	Headache	
		Grade 1–2	Grade 3	Grade 1–2	Grade 3	Grade 1–2	Grade 1–2	Grade 3	Grade 1–2	Grade 3	Grade 1–2	Grade 1–2	Grade 1–2	Grade 1–2	
0.5	1	0	0	0	0	0	0	0	0	0	1	1	1	1	
1.0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	
2.0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	
4.0	5	3	**1**	1	**1**	2	2	**1**	1	**1**	3	4	4	1	
8.0	4	3	**1**	3	0	1	0	**1**	0	0	2	0	2	2	
3.0	4	2	0	1	0	1	1	0	2	0	1	1	1	0	

[a]Hypertension ($n = 1$ grade 3 and dose-limiting), palpitations ($n = 1$ grade 1), and sinus tachycardia ($n = 2$ both grade 1)

patient had stabilization for more than 4 cycles (16 weeks), which was the maximum time any patient continued on therapy.

Discussion

Epidemiologic studies have suggested that heavy consumption of green tea may reduce the incidence and delay the onset of cancer. Preclinical studies of green tea and its polyphenolic components also suggest chemopreventive and antiproliferative effects. This phase I study was one of the first to investigate GTE in patients with an established malignancy. It showed that short-term once-daily oral administration of GTE, at 3 g/m^2 per day, is well tolerated. At this dose, the adverse effects were similar to those seen with the consumption of any caffeinated beverage, and included mild nausea, diarrhea, and anxiety.

Investigators at MDACC have also studied daily oral administration of GTE [10], determining the MTD of once-daily dosing to be 4.2 g/m^2 per day, with a toxicity profile similar to that seen in the current trial. The 25% difference in the determined MTD between the two studies is difficult to explain. In the current study, the initial patient enrolled at 4 g/m^2 per day had no significant toxicity, permitting dose escalation, to a level that proved to be above the MTD. Subsequent expansion of the 4 g/m^2 per day dose level led to two episodes of DLT among the next four patients. The MDACC group enrolled six patients at 4.2 g/m^2 per day without observing any toxicity greater than grade 2. The definition of MTD was the same in both trials. Since the same company in both trials supplied GTE, variation in pill polyphenol or caffeine content should not explain the observed differences, assuming minimal batch-to-batch variability. One possible explanation is that there may be a significant degree of interpatient variability in the toxicity that arises from exposure to GTE. The bioavailability of GTE capsules is not known, and may vary from patient to patient. The MDACC investigators found that there is considerable interpatient variation in caffeine pharmacology. It has been suggested that for compounds with such interpatient variability, accelerated dose-escalation schemes, such as used in these trials, may be misleading in terms of determination of the MTD. This arises because the lack of toxicity in any one patient does not accurately predict lack of toxicity in future patients, as would occur with compounds having less interpatient variability [2]. Greater expansion of the proposed phase II dose should minimize the risk of predicting a dose that subsequently proves to be too toxic. Due to the small numbers of patients involved, the lack of DLT seen at 4.2 g/m^2 per day (and in the current trial at 3 g/m^2 per day) may have arisen simply by chance. Despite this lack of DLT, the MDACC investigators did not recommend that once-daily dose for long-term administration. They subsequently evaluated a thrice-daily dosing schedule, and determined that 1.0 g/m^2 per dose (a total daily dose

of 3 g/m^2) was the most suitable for long-term administration, and this was their recommended dose and schedule for further study. In seven patients treated at this dose, only minor toxicities (grade 1 gastrointestinal upset, fatigue, insomnia and anxiety) were seen, similar to the toxicity seen in those treated at 3 g/m^2 per day in the current study. Thus the MTD of GTE in the current trial may be a more accurate determination of a once-daily dose likely to be tolerated for longer-term use.

The use of decaffeinated GTE preparations might reduce adverse effects and/or permit further dose escalation, and might be more suitable for long-term administration, as would be required in chemoprevention studies. However, there is evidence from preclinical studies that caffeine contributes to the inhibition of tumorigenesis seen with green tea [18]. Caffeine has been shown to enhance the tumor-inhibiting effects of doxorubicin in Ehrlich ascites carcinoma tumor-bearing mice [11]. Thus the use of decaffeinated GTE may lead to a diminished therapeutic effect.

Lower doses of GTE would likely be better tolerated. The determined MTD is not necessarily the most suitable dose for use, and a lower dose might theoretically provide the same degree of in vivo biologic activity, if one in fact exists. Disease stabilization (for 8 and 12 weeks, respectively) was seen in two of three patients treated below the MTD. In a study performed in healthy volunteers in Japan, approximately 1.3 g/m^2 per day of GTE was given daily and tolerated well; this amount is roughly equivalent to drinking ten cups of green tea per day [13]. As a decreased risk of cancer was seen in a cohort with this degree of "chronic" tea consumption [5], a daily dose of GTE of 1.5 g/m^2 per day, one-half the MTD determined in the current trial, may be sufficient to achieve the desired biological effects, assuming the biologic effect of GTE capsules is the same as that of the brewed beverage. The determination of the MTD, as historically done in phase I trials of cytotoxic chemotherapeutic agents, may not be appropriate for minimally toxic agents with purported cytostatic or chemopreventive activity. These agents may instead have a certain minimal dose required to achieve their biologic effect and above which no additional benefit is attained. As the mechanism of action of GTE is not completely understood, this desirable endpoint of an "optimal biologic dose" could not be used for this trial.

No major objective responses to GTE were seen in the current trial, while seven patients had disease stabilization lasting from 4 to 16 weeks. Similar results were obtained in the trial from MDACC, in which no major objective responses were seen. In contrast to the MDACC trial, where ten patients with stable disease were able to complete 6 months of GTE, no patient in the current trial remained on therapy for more than 16 weeks because of disease progression. While the primary endpoint of a phase I trial is safety and not response, the lack of any objective responses in a total of 60 evaluable patients (36 with NSCLC) suggests that GTE has minimal, if any, direct cytotoxic activity, especially in NSCLC. In preclinical studies, while rare complete tumor regressions have been documented [17] and both GTE and EGCG have been shown to induce apoptosis and growth inhibition in cancer cell lines [1, 8, 14], there is little evidence that either GTE or EGCG has significant cytotoxic activity. Adding EGCG to cultured PC-9 cells inhibited their growth, but removal of EGCG from the medium then led to an increase in cell number, suggesting a cytostatic effect [8]. Administration of GTE and EGCG to mice with established skin papillomata did not lead to any histopathologic evidence of cytotoxicity of the compounds [17]. However, the effects of standard cytotoxic [11] or hormonal [14] agents may be enhanced by green tea.

Future studies of GTE should focus on these cytostatic and chemotherapy-enhancing properties, and on the purported chemopreventive activity. The study of GTE as a chemopreventive agent in lung cancer is warranted given the preclinical data showing inhibition and apoptosis of lung cancer cell lines [8, 14] and the inhibition of tobacco-induced lung tumors in mice [16]. Single-agent GTE might be studied as a means to prevent or delay relapse following completion of therapy for earlier-stage lung cancer, or as a chemopreventive agent in patients at high risk for second primary smoking-related cancers. The toxicity profile of longer-term use of GTE could be determined in these patients, unlike those with established malignancies. EGCG has also been shown to inhibit the Her-2/neu signaling pathway and inhibit the growth of the Her-2/neu overexpressing cell line NF639 [9], and thus there could be a role for GTE in the chemoprevention of breast cancer, or in the treatment of breast cancers overexpressing Her-2/neu. Finally, since it is well tolerated, GTE could be studied in combination with standard cytotoxic agents in advanced lung cancer. Further study of GTE as a single-agent in advanced, established malignancies, particularly NSCLC, may not be warranted in the absence of greater preclinical evidence of cytotoxic activity.

In conclusion, this study has determined that the MTD for oral, once-daily GTE is 3 g/m^2 per day. Given the preclinical data, studies of GTE as a single agent should enroll those at high risk for relapse following definitive treatment of their malignancy or those at high risk of developing a second cancer. Given its mild toxicity, the study of GTE in combination with cytotoxic chemotherapy in patients with advanced malignancies is also warranted.

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