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Clinical effects of oral green tea extracts in four patients with low grade B-cell malignancies

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Abstract

Green tea or its constituents have long been touted as a health promoting substance including claims it may have cancer prevention properties. We previously reported the in vitro ability of one tea polyphenol, epigallocatechin gallate (EGCG), to induce apoptotic cell death in the leukemic B-cells from a majority of patients with chronic lymphocytic leukemia (CLL). After the publication of our findings many patients with CLL and other low grade lymphomas began using over-the-counter products containing tea polyphenols despite the absence of evidence to suggest clinical benefit, definition of possible toxicities, or information on optimal dose and schedule. We have become aware of four patients with low grade B-cell malignancies seen in our clinical practice at Mayo Clinic who began, on their own initiative, oral ingestion of EGCG containing products and subsequently appeared to have an objective clinical response. Three of these four patients met criteria for partial response (PR) by standard response criteria. Although spontaneous remission/regression is occasionally observed in individuals with low grade B-cell malignancies, such events are rare. Several patients presented here had documented steady clinical, laboratory, and/or radiographic evidence of progression immediately prior to initiation of over-the-counter green tea products and then developed objective responses shortly after self-initiating this therapy. Such anecdotes highlight the need for clinical trials of tea polyphenols to define the optimal dosing, schedule, toxicities, and clinical efficacy before widespread use can be recommended. An NCI sponsored phase I/II trial of de-caffeinated green tea extracts for patients with asymptomatic, early stage CLL opened at Mayo Clinic in August 2005.

Keywords: Green tea; EGCG; CLL; Lymphoma

1. Introduction

Green tea or its constituents have long been touted as a health-promoting substance with claims of cancer prevention properties. Recent studies have more precisely identified the active chemical compounds in green tea that may mediate these effects. These compounds are as a group termed tea polyphenols or catechins [1]. In March 2004, we reported the in vitro ability of one tea polyphenol, epigallocatechin gallate (EGCG), to induce apoptotic cell death in the leukemic B-cells from a majority of patients with chronic lymphocytic leukemia (CLL) [2]. EGCG also reduced levels of the protein Mcl-1, an anti-apoptotic protein of known importance in CLL B-cell resistance to apoptosis [3,4], at doses as low as 0.68 μM. The serum concentration of EGCG achieved by tea drinkers is between 0.1 μM and 1.0 μM [5–7]. Our findings suggested EGCG's effect on CLL B-cells was, at least in part, mediated through its affects on the VEGF receptor [2]; however, a multiplicity of other biologic mechanisms for EGCG effects on tumor cells has also been proposed [1,8,9].

Most low grade, B-cell malignancies are incurable with current treatments, and asymptomatic patients with these illnesses are often managed with what physicians term "watchful waiting" [10]. After the publication and subsequent dissemination of our findings with EGCG in CLL by the lay press [11], some patients with CLL and other low grade lymphomas began using over-the-counter products reported to contain tea polyphenols despite the absence of evidence on

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clinical benefit, toxicity, or knowledge of optimal dose and schedule.

2. Methods

Based on feedback from colleagues and our patients, we become aware of several patients with low grade, B-cell malignancies seen at Mayo Clinic who, of their own initiative, began oral ingestion of EGCG containing products and appeared to objectively derive clinical benefit. With IRB approval, patient charts were subsequently abstracted for the clinical details regarding diagnosis and clinical course prior to and after initiating green tea containing products. Patients were contacted to clarify, as much as possible, the preparation, quantity, frequency of use of green tea products, and to update our records with recent blood counts from outside laboratories. Here, we present four patients who we believe have evidence of clinical benefit from these products.

2.1. Patient 1

A 58-year-old woman, with a history of hypertension and post-polio syndrome, was incidentally noted to have a slightly elevated absolute lymphocyte count ($4.67 \times 10^9\,L^{-1}$) in June 2001. Immunophenotyping of peripheral blood lymphocytes demonstrated a clonal population of B-cells expressing CD5, CD23, and dim surface immunoglobulin. Adenopathy on staging CT scan was primarily limited to the bilateral axillary regions (largest node 1.5 cm × 2.5 cm) with subtle adenopathy (between 1 cm and 2 cm) also noted in abdomen and inguinal regions. The patient was categorized as having the small lymphocytic lymphoma (SLL) variant of CLL/SLL [10,12]. She had no constitutional symptoms or significant cytopenias and was managed with observation. Over the ensuing 29 months, the patient had a progressive increase in lymphadenopathy (largest node 3 cm × 4 cm on CT scan November 2003), but there was no significant change in her absolute lymphocyte count (ALC) (range 1.1×10^9–$5.2 \times 10^9\,L^{-1}$). A bone marrow biopsy obtained during February 2003 (20 months after diagnosis) demonstrated 20–25% marrow involvement by CLL/SLL B-cells. Cytogenetic analysis by fluorescent in situ hybridization (FISH) demonstrated these cells carried the trisomy 12 abnormality.

After hearing reports regarding the in vitro effects of tea polyphenols on CLL B-cells, the patient started taking an over-the-counter green tea capsule labeled as containing 315 mg of tea polyphenols twice per day beginning in March 2004 (33 months after diagnosis). Over the next 12 months, she demonstrated a steady clinical and radiographic decline in her lymphadenopathy with >50% reduction in bilateral axillary nodes (Fig. 1) and near normalization in the size of all other areas of adenopathy. The patient's reduction in lymph node size met the NCI criteria for a partial response (PR). She continues to do well taking daily oral tea polyphenol capsules

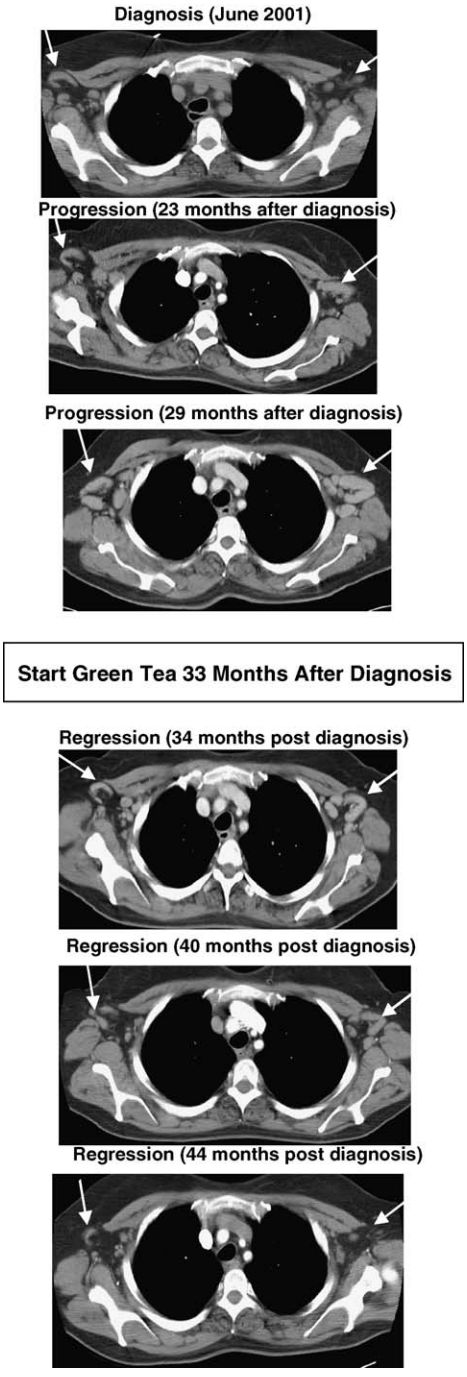

Fig. 1. Fifty-eight-year-old woman with CLL/SLL: serial CT scans prior to and after initiation of green tea containing products.

44 months after diagnosis and has not required conventional therapy.

2.2. Patient 2

A 55-year-old woman was evaluated for asymptomatic cervical adenopathy in March 2003. Excisional node biopsy demonstrated a grade 1, follicular B-cell lymphoma with a clonal population that expressed CD 19, CD20, CD 10

(dim), and CD23. CT of the chest, abdomen, and pelvis demonstrated a 1.7 cm × 2.0 cm left axillary node and multiple mesenteric nodes at the upper limit of normal size. LDH was normal and bilateral bone marrow biopsies demonstrated 5% marrow involvement of follicular lymphoma. The patient was categorized as having stage IV disease and observation was recommended. Follow-up CT scans in November 2003 (8 months after diagnosis) and May 2004 (14 months after diagnosis) demonstrated measurable progression of lymphadenopathy in the left axilla (largest node 3.0 cm × 2.3 cm) and mesentery (∼2.7 cm × 1.2 cm). The patient remained asymptomatic and continued observation was recommended.

After hearing reports regarding the in vitro effects of green tea extract on CLL B-cells, the patient began drinking a cup of green tea each day (prepared with two tea bags) starting August 2004 (∼17 months after diagnosis). Follow-up CT scans in November 2004 (20 months after diagnosis) and June 2005 (27 months after diagnosis) demonstrated a >50% decrease in the sum of the products of the six largest lymph node areas consistent with a PR according to the International Working Group [13] criteria for non-Hodgkins lymphoma (Fig. 2). She continues to do well drinking green tea daily 27 months after diagnosis and has not required conventional therapy.

2.3. Patient 3

A 50-year-old woman with sleep apnea, depression, and history of resection of a benign parotid tumor had incidental diagnosis of Rai stage 0 CLL in February 1999 (ALC $10.5 \times 10^9\,L^{-1}$). The patient had no clinical symptoms and was observed over the next 5 years with a slow increase of her ALC. In approximately January 2004, she developed fatigue and night sweats. Her WBC was $32.1 \times 10^9\,L^{-1}$ and ALC was $20.4 \times 10^9\,L^{-1}$. A marrow biopsy was obtained and demonstrated 5% involvement by CLL B-cells. A CT scan of her chest/abdomen/pelvis at that time did not demonstrate any adenopathy or splenomegaly.

The patient had heard reports regarding the in vitro effects of green tea extract on CLL B-cells and started using a green tea patch (labeled as containing 300 mg polyphenols) daily as well as drinking three green tea packets each day (labeled as containing 300 mg of polyphenols in each packet) in April 2004 (62 months after diagnosis). One month later, the patient's WBC was $26.6 \times 10^9\,L^{-1}$ and her ALC was $17.2 \times 10^9\,L^{-1}$. No change in clinical symptoms was noted; however, the patient's night sweats resolved after discontinuing escitalopram oxalate used for treatment of depression. The patient discontinued the patch but continued drinking one green tea packet per day. In July 2004, she came to Mayo Clinic for a second opinion regarding her constitutional symptoms. ZAP-70 testing and CD38 testing at that time were both negative. The patient's constitutional symptoms were not deemed to be secondary to CLL and continued observation was recommended. She continued drinking one packet of green tea per day. Over the following 11 months, she had a sustained decline in her ALC (Fig. 3). Despite this decline in ALC, she would be classified as having stable disease according to the NCI criteria. She continues to do well without conventional therapy now 77 months from diagnosis.

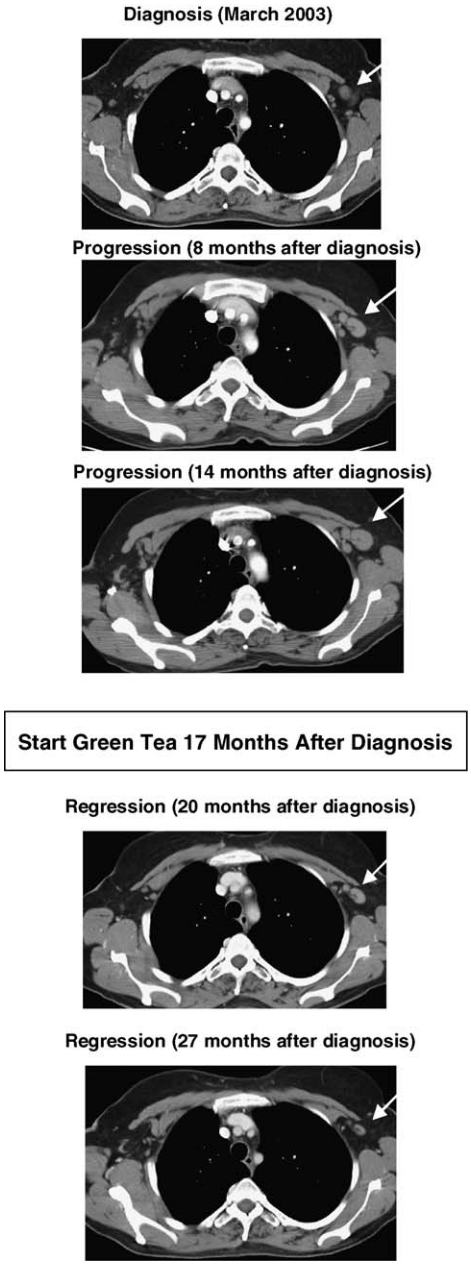

Fig. 2. Fifty-five-year-old woman with follicular lymphoma: serial CT scans prior to and after initiation of green tea containing products.

2.4. Patient 4

A 60-year-old woman with a history of hypertension, hypothyroidism, and osteoporosis had an incidental diagnosis of asymptomatic Rai stage 0 CLL in July 1995 (ALC

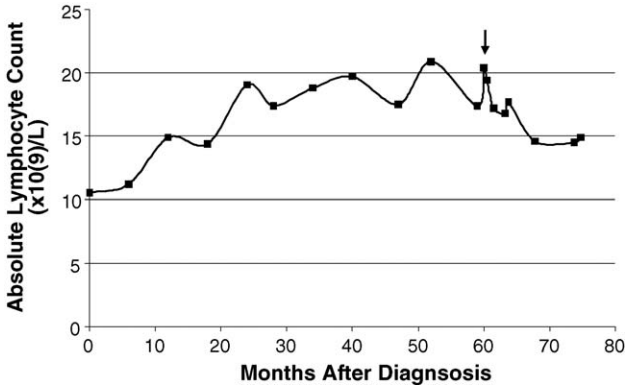

Fig. 3. Fifty-year-old woman with CLL. Arrow indicates the date of initiation of green tea. All blood counts were done in the same laboratory.

$7.68 \times 10^9\,L^{-1}$). She was observed over the next 5 years and remained asymptomatic. Prognostic factor testing in July 2000 showed that the patient's CLL B-cells were CD38 negative, immunoglobulin heavy chain variable gene status was mutated, and had deletion of 13q- by FISH testing. ZAP-70 testing at a later time point (7/05) was negative. The patient was continued on surveillance. In August 2004 (109 months after diagnosis), her WBC and ALC increased to $24.2 \times 10^9\,L^{-1}$ and $12.6 \times 10^9\,L^{-1}$, respectively.

The patient was very concerned by this increase in the blood ALC. She had heard reports regarding the in vitro effects of green tea extract on CLL B-cells, and began drinking eight cups of green tea per day. One week later, her WBC was $18.1 \times 10^9\,L^{-1}$ and ALC was $10.0 \times 10^9\,L^{-1}$. She continued drinking eight cups of green tea daily with further decline in her ALC over the following 4.5 months (Fig. 4). Based on her 50% reduction in ALC she would be classified as a PR according to the NCI criteria. In April 2005, the patient was started on methotrexate and prednisone by her home physicians for treatment of arthritis making interpretation of subsequent blood counts difficult. She is still asymptomatic from her CLL 120 months from diagnosis and continues to drink green tea daily.

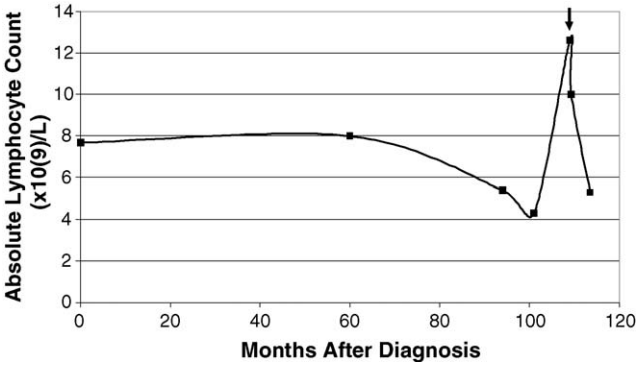

Fig. 4. Sixty-year-old woman with CLL. Arrow indicates the date of initiation of green tea.

3. Discussion

In total, our report on these patients with low grade B-cell malignancies adds to the growing evidence that food products that contain polyphenols have anti-tumor activity. In fact, the polyphenol containing agents have not only been shown to have anti-tumor activity but have been linked to chemoprevention of human tumors. A number of epidemiologic studies have linked consumption of green tea to a decreased risk of cancer. A wide range of animal models has also supported green tea's ability to prevent tumorigenesis [1]. Multiple mechanisms have been proposed as the explanation of the effect of green tea, including anti-angiogenic properties [14–16], DNA damage [17,18], and inhibition of telomerase [1,9]. More recent studies of EGCG suggest this agent may affect folate metabolism [19], suppress transcription factors leading to cell-cycle arrest [2,14,19–30], and induce oxidative stress through generation of ROS [19–30]. In vitro studies have also shown EGCG decreases levels of anti-apoptotic proteins [2,31] at drug levels which are achieved in the serum of tea drinkers in vivo [5–7].

In addition to our published work in CLL showing that EGCG can induce apoptosis in CLL B-cells, tea polyphenols were recently reported to induce caspase-3 dependent apoptotic cell death in primary acute myeloid leukemia cells and malignant B-cell cell lines through a mechanism dependent on ROS generation [23]. Similar to our findings in primary CLL B-cells, EGCG treatment was associated with down-regulation of Mcl-1 but not Bcl-2 [23]. These investigators also demonstrated that in vivo treatment with EGCG induced apoptosis of AML cells in a mouse model [32]. Two groups have reported that EGCG induces apoptotic cell death in primary human myeloma cells [23,24]. Interestingly, the potential clinical efficacy of green tea as a chemopreventative agent was recently suggested in a double-blind, placebo-controlled trial of EGCG capsules for treatment of men with high-grade, prostate intraepithelial neoplasia. This study found only 3% of men taking EGCG developed prostate cancer after 1 year of follow-up versus 30% of men assigned to placebo [33].

Several recent studies explored the safety and toxicity of pharmacologic doses of EGCG in healthy individuals [34,35]. One study of decaffeinated, purified EGCG as daily oral therapy for 4 weeks (400 mg, p.o., BID or 800 mg, q.d.) reported only mild, adverse effects (excess gas, stomach ache, upset stomach, nausea, abdominal pain, headache, muscle pain, and dizziness) which, with the exception of grade 1 nausea, were similar in frequency and severity to those experienced by individuals receiving placebo [34]. No toxicities greater than grade 1 were observed. The plasma concentration of free EGCG could be increased five-fold when taken in fasting conditions rather than with food [36]. In another study of a single, oral dose of EGCG in 60 healthy adults, no toxicity was observed in 10 patients treated at the highest dose tested, 1600 mg [35].

Toxicity at relatively high doses also appears to be mild in patients with malignancy. Thus, a phase I, dose escalation study using green tea extract (GTE) treatment in patients with incurable solid tumors found generally mild to moderate toxicity at most dose levels in 49 patients treated for up to 6 months with GTE. This study used once daily and three times daily dose schedules. Doses ranged from 0.5 g/m^2 to 5.05 g/m^2 on the once daily schedule and 1 g/m^2 to 2.2 g/m^2 on the three times daily schedule. Dose limiting toxicities (DLT) in this study were gastrointestinal and neurologic (agitation, insomnia, and memory difficulties), and were attributed to caffeine in the preparation used rather than tea catechins [37]. To the best of our knowledge, none of the patients we report here experienced adverse effects attributed to green tea containing products.

Spontaneous remission/regression can occur in individuals with low grade B-cell malignancies, including CLL/SLL, although the frequency of such events appears to be rare [38–40]. Additionally, many of the patients labeled as having a "spontaneous" remission/regression in prior reports actually received conventional therapy prior to regression [40]. In contrast, several patients in this report had documented steady clinical, laboratory, and/or radiographic evidence of disease progression immediately prior to initiating over-the-counter green tea products and had objective responses shortly after starting this therapy. Three of the patients reported here (patients 1, 2, and 4) met criteria for a partial response according to standard criteria (NCI criteria [10] for patients with CLL and International Working Group Criteria [13] for patient with follicular lymphoma). Patient 3 would be classified as having stable disease despite her reduction in ALC. The timing of these responses suggests to us that they occurred due to the use of tea polyphenols rather than a spontaneous regression. None of these four patients had dramatic changes in other medications or occurrence of any other significant medical illness at the time of their green tea/EGCG associated responses. The literature would suggest that observing four such regressions at a single medical center in an 18 month time interval, all by chance occurring in conjunction with initiation of green tea containing products, would be unusual [38].

We are not able to confirm the exact type or amount of polyphenol taken by each patient. Over-the-counter herbal supplements are not considered pharmacologic agents by the U.S. Food and Drug Administration and their content is not regulated. The products ingested by the individuals presented here were labeled as green tea/EGCG containing products; however, there is no verification between the labeled amount of tea polyphenols these preparations are reported to contain and their actual polyphenol content. Furthermore, since we do not routinely question patients on their use of green tea containing products, we do not know the number of patients in our practice who used green tea/EGCG and it is therefore not possible to estimate what percentage of patients taking such products had experiences similar to the individuals presented here.

These anecdotes cannot determine the effectiveness of tea polyphenols, and highlight the need for clinical trials to define the optimal dosing, schedule, toxicities, and clinical benefits before widespread use can be recommended. An NCI sponsored phase I/II trial of de-caffeinated green tea extract for treatment of patients with asymptomatic, early stage CLL opened at Mayo Clinic in August 2005.

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