Evidence for and Against Green Tea and Turmeric in the Management of Chronic Lymphocytic Leukemia

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Abstract

Complementary and alternative medicine (CAM) is a diverse group of medical and health care systems, practices, and products that are not generally considered part of conventional medicine. Chronic lymphocytic leukemia (CLL) is the most common leukemia diagnosed in the western hemisphere, and 16.5% to 66% of patients have reported using CAM. Most patients use spiritual/mind–body techniques and high doses of vitamins and herbs (most commonly polyphenols, including teas). We have reviewed the reported data on green tea and turmeric use in CLL patients.

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Introduction

Complementary and alternative medicine (CAM) is becoming an increasingly used approach by patients to address their health and their malignancy. CAM has been defined by the National Institutes of Health National Center for Complementary and Alternative Medicine as a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.[1] CAM consists of natural products, mind-body therapies, body manipulation, and energy therapies.[1] It is estimated that 15% to 77% of cancer patients are actively using CAM.[2-19] A recent meta-analysis of cancer patients and CAM use in 18 countries and > 65,000 patients showed a current use of 40%, with the greatest prevalence in the United States, and an overall increase in CAM use from 25% in the 1970s to 49% after 2000.[8]

The use of CAM tends to increase after a diagnosis of a malignancy,[5,9] with the aim of increasing general health and well-being and augmenting the body's ability to fight cancer.[2,4,5,11-13,15] Patients report using spiritual/mind-body techniques and high doses or combinations of vitamins and herbs (most commonly polyphenols, including teas).[2,6,9-12,15,16,18] Most patients report that their information on CAM has come from family, friends, or the media, although they also identified the information they had received from their physician as the most important.[2,5,7,10-13,15-18,20] In a recent survey of health care professionals, most professionals reported they did not have adequate knowledge nor were up to date on the evidence of CAM use in oncology.[7]

Chronic lymphocytic leukemia (CLL) is the most common leukemia diagnosed in the Western world.[21] Although reports of CAM use in CLL range widely from 16.5% to 66%,[2,20,22] 1 large survey of 1147 American CLL patients found a 66% usage rate.[22] Similar to other malignancies, polyphenols, including green tea and turmeric, vitamin supplementation, and mineral supplementation were most commonly used.[2,20,22] In 1 survey of CLL patients, 59% had decided to use CAM based on information they found on the internet without consulting their physician.[20] With the high usage of CAM by patients with malignancies such as CLL, it is important for physicians to understand the current data involving these agents such as green tea and turmeric. The present review provides a summary of the current evidence relating to green tea and turmeric use by CLL patients.

Materials and Methods

The data were collected by searching PubMed and Google Scholar on May 3, 2018. The search terms were "complementary and alternative medicine and chronic lymphocytic leukemia," "alternative medicine and chronic lymphocytic leukemia," "green tea and chronic lymphocytic leukemia," "EGCG and chronic

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lymphocytic leukemia," "turmeric and chronic lymphocytic leukemia," and "curcumin and chronic lymphocytic leukemia." All English, in vivo, in vitro, and clinical trials relevant to green tea and turmeric use in CLL were included.

Green Tea

Background

Green tea, brewed from the leaves of the *Camellia sinesis* plant, has been consumed for centuries for its purported medicinal benefits.[23] It is available as a highly concentrated extract that can be easily accessed by the public at local grocery stories, pharmacies, and health food stores.[23] It is a potent antioxidant and has been suggested to have antimicrobial, cardioprotective, neuroprotective, antidiabetic, and anticancer effects.[24-26]

The active compounds found in green tea are polyphenols, the major group consisting of catechins.[23,24,27] The most bioactive polyphenol is epigallocatechin-gallate (EGCG). Multiple potential anticancer effects of green tea have been cited, including antiangiogenic properties, cell cycle arrest, effects on folate metabolism, effects on DNA damage, inhibition of telomerase, reductions in the level of antiapoptotic proteins, proteasome inhibition, the generation of reactive oxygen species, and demethylating/epigenetic effects.[28-30]

Mechanism of Action

The activity of green tea in CLL has not been fully elucidated. One mechanism cited is increased apoptosis secondary to downstream inhibition of antiapoptotic proteins.[31] It is thought that the vascular endothelial growth factor (VEGF) autocrine pathway in CLL leads to a prosurvival environment through increased antiapoptotic proteins, including MCL-1, XIAP, Bcl-2, and Bcl-2A1. An in vitro study of CLL cells taken from untreated donor patients and cultured with EGCG found downregulation of the phosphorylation status of both VEGF receptor (VEGFR)1 and VEGFR2 and the total secreted VEGF. This was associated with decreased levels of MCL-1 and XIAP and a dose-dependent induction of apoptosis with the level of cell death $> 80\%$ at EGCG concentrations as low as 20 μM.[31] It has also been suggested that EGCG might lead to downstream inhibition of antiapoptotic proteins through the inhibition of the phosphoinositide-3 kinase (PI3K)/Akt pathway. Ponath[32] analyzed the cells from donor CLL patients cultured with EGCG and co-cultured with primary human bone marrow stromal cells. Ponath[32] found that exposure to EGCG was associated with the downregulation of the catalytic and regulatory domain of PI3K, a decrease in the phosphorylation of Akt and decreased expression of Bcl-2 and MCL-1. EGCG was also shown to impede chymotrypsin-like activity in CLL cells, leading to proteasome inhibition and early apoptosis. CLL cells co-cultured with bone marrow stromal cells were less sensitive to EGCG and a cytotoxic effect was only observed at concentrations of ≥ 200 μM.[32]

In both cited studies and an in vitro study of primary lymphoma cells from 7 patients and from 5 established human B-cell lymphoma lines (HT, DOHH2, KARPAS, Ramos, RL) exposed to EGCG, evidence of increased PARP cleavage and decreases in caspase-3 were noted after exposure to EGCG, suggesting the mechanism of cell death was related to augmentation of the apoptotic process.[31-33] At present, green tea is hypothesized to promote apoptosis through downregulation of the VEGF autocrine pathway, PI3K/Akt pathway, and proteasome activity.[34]

Green tea, and its components, has also been thought to induce apoptosis in B-cell lymphomas through the production of reactive oxygen species (ROS). One study evaluated B-cell lymphoma cells from either 7 patient donors or from 1 of 5 established lymphoma cell lines (HT, DOHH2, KARPAS, Ramos, RL). The cells were exposed to EGCG and had been cultured with and without catalase 30 minutes before EGCG exposure. Pretreatment with catalase provided protection against cell death in both primary lymphoma cells and cell lines, suggesting EGCG-induced cell death is dependent on ROS generation.[33] Another study using human B-cell lines, including myeloma cells (IM0, RPMI8226, U266) and Burkitt lymphoma cells (HS-sulta) cultured with EGCG, found that EGCG was associated with the loss of mitochondrial transmembrane potentials, the release of cytochrome-c, Smac/DIABLO, and apoptosis-inducing factor from the mitochondria, and activation of caspase-3 and caspase-9, leading to apoptosis. Although not studied in CLL cells directly, these studies allude to ROS as a potential result of EGCG in B-cell lymphomas.

Another potential effect of green tea on CLL is through the downregulation of regulatory T-cells (T-regs). T-regs are a subset of $CD4^+$ T lymphocytes that suppress the induction of effector T cells and ultimately maintain tolerance to self-antigens and prevent autoimmune disease.[34] Increased levels of T-regs have been associated with the development and progression of many cancers, including CLL, owing to inhibition of the T-cell antitumor response.[27,35,36] One study of CLL cells harvested from 4 untreated CLL patients and from healthy controls exposed to increasing doses of EGCG (0, 25, 50, 75, or 100 μg/mL) found that healthy control cells did not experience apoptosis but 90% of CLL B cells and virtually all T cells underwent apoptosis at the maximum concentration of EGCG.[37] This suggests that the apoptosis in CLL B cells can be partially explained by the loss of T-cell protection. A small prospective study of 12 Rai stage 0 to 2 CLL patients and 12 healthy controls exposed to green tea extract capsules evaluated the role of EGCG and T-regs in CLL patients. Patients received 4 capsules, each containing 767 mg of green tea leaves and 31.5 mg of EGCG, daily for the first month and 6 capsules daily for the next 5 months. Two CLL patients withdrew from the study after 2 weeks because of tachycardia and abdominal pain and 2 controls withdrew from the study because of abdominal pain after 20 and 30 days, respectively. Of the 10 subjects who completed the study, 8 showed a reduction of lymphocytosis and absolute number of circulating T-regs, 1 had stabilization of lymphocytosis and reduction of T-regs, and 1 showed an increase in both. Also, both interleukin-10 and transforming growth factor-β were decreased, further supporting a potential role for green tea as an immune modulator.[27] The major effects experienced were abdominal pain (1 patient, 2 controls), flatulence (2 patients, 2 controls), and tachycardia (1 patient). No deaths were reported.

Drug Interactions

In in vitro studies, EGCG has also been shown to interact with various antineoplastic agents. A study of primary CLL cells treated with various doses of fludarabine, chlorambucil, or fludarabine and

chlorambucil, with or without EGCG (50-100 μM), found that the LD50 (lethal dose that killed 50% of the test sample) was 100 μM. In co-titration experiments, EGCG had an additive or synergistic effect on apoptosis when combined with chlorambucil in most patients (13 of 15; 2 of 15 showed antagonism). EGCG also had primarily additive or synergistic effects when added to the fludarabine and chlorambucil group (8 of 10; additive in 7 and synergism in 1). However, in the fludarabine group, the results varied more, with 8 of 18 patients having antagonistic effects, 4 of 18 having additive effects, and 6 of 18 having synergistic effects. When these groups were exposed to a set dose of 4 μM of EGCG, EGCG had an additive or synergistic effect in most samples in all 3 groups (chlorambucil, 11 of 14; fludarabine, 13 of 16; fludarabine and chlorambucil, 10 of 10).[38]

In contrast, another study using both a mouse model and multiple myeloma cell lines (RPMI/8226 and U266) found that EGCG blocked proteasome inhibition by bortezomib both in vitro and in vivo. When myeloma cell lines were cultured with both bortezomib and EGCG, cell survival remained 100%. This was also found when RPMI/826 multiple myeloma cells were implanted subcutaneously into nude mice and subsequently treated with bortezomib and EGCG alone or in combination. Bortezomib alone led to a significant increase in apoptosis, and animals treated with EGCG alone or with both EGCG and bortezomib demonstrated no increase in apoptotic cell death. Also, although EGCG has been shown to have antiproteasome activity, bortezomib is significantly more potent, with 10 nM of bortezomib killing an entire cell culture of multiple myeloma cells within 48 hours and 10 μM of EGCG, during the same time period, having no effect on cell survival.[32]

It is also important to note that green tea and its components inhibit CYP450 isozymes (CYP3A4, CYP1A1, and CYP1A2), P-glycoprotein−mediated transport, and UGT1A1. Also, its tannin content interferes with the intestinal absorption of some nutrients and drugs.[24] Ultimately, we have very limited research and understanding of how EGCG interacts with accepted CLL treatment algorithms.

Clinical Trials

In a phase I portion of a phase I/II clinical trial assessing the effects of green tea in untreated asymptomatic Rai stage 0 to 2 CLL patients, 33 patients were given Polyphenon E capsules containing approximately 200 mg of EGCG. The patients were separated into 8 dose levels ranging from 400 to 2000 mg. The maximum tolerated dose was not reached. Two patients experienced drug-limiting toxicities, which consisted of grade 2 dysphagia during cycle 1 at a 1200-mg dose and grade 2 sweating, flatulence, abdominal distension, and nausea during cycle 1 at 2000 mg. Five patients (15%) experienced a grade 2 event (3 nausea, 2 anorexia, 2 diarrhea, 2 flatulence, 1 fatigue) and 2 patients (6%) experienced a grade 3 event (1 abdominal pain, 1 diarrhea). The most common adverse effects were nausea (grade 1, 39%; grade 2, 9%), transaminitis (grade 1, 33%), abdominal pain (grade 1, 30%; grade 3, 3%), anorexia (grade 1, 27%; grade 2, 6%), and diarrhea (grade 1, 18%; grade 2, 6%; grade 3, 3%). The response was measured using the National Cancer Institute Working Group criteria.[39] Only 1 patient achieved a partial remission. Additionally, 11 patients (33%) had a $>$ 20% reduction in their absolute leukocyte count (ALC) for $\geq$ 2 months. Of the 12 patients who presented with palpable lymphadenopathy, 11 experienced at least a 50% reduction in the sum of the products of all nodal areas, determined by physical examination.[29]

The phase II component of the trial conducted by Shanafelt et al[40] evaluated 6 patients who had been previously treated, in addition to the original 36-patient untreated cohort. The patients received Polyphenon E capsules containing ~200 mg of EGCG at a dose of 1000 mg orally twice daily for the first 7 days of cycle 1 and then 2000 mg orally twice daily for 6 months. Of the 42 patients, 13 (31%) required a dose reduction. The most common side effects were nausea (grade 1, 55%; grade 2, 5%), diarrhea (grade 1, 45%; grade 2, 4%), transaminitis (grade 1, 31%; grade 2, 14%; grade 3, 2%), and flatulence (grade 1, 31%; grade 2, 5%). Of the 42 patients, 18 (43%) experienced a grade 2 event (3 nausea, 3 abdominal pain, 6 transaminitis, 1 anorexia, 4 diarrhea, 1 dyspepsia, 2 flatulence, 3 fatigue) and 3 (7%) a grade 3 event (1 abdominal pain, 1 transaminitis, 1 fatigue). Twelve patients discontinued therapy early (9 because of adverse events and 3 because of disease progression).[40] Only 1 patient had a partial remission (overall response rate, 2.4%); 30% of patients had a decline in their ALC of $>$ 20% for $\geq$ 2 months, and ~70% of those with lymphadenopathy experienced a $>$ 50% reduction in the sum of products during treatment as determined by physical examination.[40]

Toxicity

The US Pharmacopeia (USP) evaluates over-the-counter supplements for manufacturing standards, adulteration, and contamination. These standards and reference materials are recognized in the United States and 130 other nations worldwide.[41,42] The USP Dietary Supplements Information Expert Committee (DSI EC) is a council of experts who establish a safety classification for dietary supplements.[42] In 2008, the USP performed a systematic review of the safety of green tea extract after French and Spanish authorities suspended market authorization for Exolise, a weight loss product containing a hydroalcoholic extract of green tea, after 13 reports of associated liver injury, 1 of which resulted in liver failure.[42] In that review, 216 adverse event reports were identified, 34 were nonduplicate cases related to liver injury, of which 27 were given a Naranjo score of possible and 7 a score of probable. The report also indicated which products were implicated.[42] Of the identified products, they differed in terms of their composition, solvent of extraction, dose, and duration of use, and only 1 report analyzed the product composition. In the Food and Drug Administration MedWatch search, 37 reports were excluded because the product also contained ephedra. The data also noted 18 reports of associated vomiting, diarrhea, or abdominal pain, 18 reports of rash or allergy, 5 reports of packaging issues, and 9 reports of microbial contamination. The common adverse events reported included dehydration, rash, nausea, vomiting, headache, abdominal pain, heart palpitations, fever, headache, tremors, elevated blood pressure, dizziness, chest tightness, and hot flashes.[42]

Ultimately, the DSI EC decided to assign green tea extract a class 2 safety score, suggesting "the DSI EC is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately, provided there is a

warning statement in the labeling section." The labeling statement that USP requires is as follows: "Take with food. Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice."[42]

More recently, a meta-analysis of 34 randomized controlled trials of green tea extract assessed the association of liver toxicity and green tea. The study identified only 4 trials reporting liver-related adverse events involving 7 subjects (8 events) in the treatment group and 1 subject (1 event) in the control group. The calculated odds ratio for intervention versus placebo was 2.1 (95% confidence interval, 0.5-9.8). Most events reported were for elevations in liver enzymes, and no serious liver-related adverse events were reported. Their conclusion was that liver toxicity after intake of green tea extract is rare.[43]

A recent review conducted in 2018 of the toxicity of green tea extract concluded that the most severe side effects of green tea and its constituents were hepatoxicity and gastrointestinal disturbance (abdominal pain, vomiting, diarrhea). That review, similar to the USP, concluded that green tea-based substances should be avoided by patients with liver disease. It has been recommended that green tea extract should be ingested with food after noting increased bioavailability when consumed on an empty stomach, leading to increased toxicity.[24]

Conclusion

From the reported data, our current recommendation is to avoid green tea, both as EGCG and as an extract, usage by CLL patients, especially those with any history of liver or gastrointestinal disease or receiving CLL-directed therapy. The current research for green tea in CLL has demonstrated minimal activity in terms of objective responses, mostly in asymptomatic, early-stage patients who would not normally warrant CLL-directed therapy by the International working group CLL criteria.[44] In addition, the current data support the occurrence of significant adverse events (even with limited exposure) associated with green tea, especially its extracts and EGCG. This is especially concerning when most patients who consume green tea extracts/EGCG are asymptomatic from the perspective of their underlying disease. At present, we could not identify ongoing trials for green tea or green tea extract in CLL patients.

Turmeric

Background

Curcumin is a natural polyphenol derived from turmeric (*Cucuma longa*).[45,46] It is a key ingredient in curry and has been used as a medicinal substance for centuries. It has been suggested to have potential benefits for sinusitis, allergy, asthma, cough, hepatic disease, coryza, bronchial hyperactivity, wound healing, Alzheimer disease, and heart disease.[46,47] It has been proposed to have antioxidant, anti-inflammatory, and antitumor properties.[45-48]

The anticancer effects of curcumin appear to be multimodal and include regulation of various transcription factors, including AP-1, PPAR-γ, NF-κB, Nrf2, and STAT3, inhibition of many proinflammatory cytokines, including tumor necrosis factor-α, downregulation of oncogenic kinases, including Iκbα, MAPKs, cyclin D1, p53, and ERK1/2, and induction of the glutathione-S-transferase and quinine reductase system that neutralize reactive oxidative stress.[46-48]

Mechanism of Action

Inhibition of NF-κB signaling has been shown to be particularly important in CLL.[45,49] NF-κB is a protein complex that regulates DNA transcription, cytokine production, and cell survival.[49-51] It is known to induce COX-2 expression, which causes resistance to apoptosis and inflammation.[52] It is also critical in the transcription of many prosurvival proteins such as c-Myc and EGR1.[45,53] Nuclear NF-κB is constitutively active in CLL cells.[45,49] In vitro analyses of CLL cells exposed to curcumin have shown a decrease in the quantity of nuclear NF-κB.[45] Further studies using primary CLL cells revealed that curcumin exposure was associated with the phosphorylation of IκBα. Dephosphorylation of IκBα is required for the separation of NF-κB from IκB and its translocation from the cytoplasm to the nucleus. Therefore, the phosphorylation of IκBα inhibits the activity of NF-κB.[49] Other prosurvival proteins such as XIAP and Mcl-1 were also downregulated, which was thought to be secondary to the downstream effects of inhibition of NF-κB translocation into the nucleus.[49] The same study found curcumin exposure was associated with increased phosphorylation of both STAT3, another constitutively active prosurvival protein in CLL, and Akt.[49] The proapoptotic protein BIM, involved in the inhibition of Akt, was also elevated.[49]

B-cell lymphoma cells (BKS-2 and WEHI-231) exposed to various concentrations of curcumin were also associated with increased apoptosis and downregulation of EGR1, c-Myc, Bcl-X_L, and p53 expression.[53] Ultimately, it is thought that curcumin inhibits many of the constitutively active prosurvival proteins found in CLL, including NF-κB and STAT3, and promotes proapoptotic activity through upregulation of BIM.

However, CLL cells observed in association with human bone marrow stromal cells were resistant to the proapoptotic effects of curcumin. Curcumin levels of 20 μM were required to achieve apoptosis, which are not obtainable in vivo.[49]

Drug Interactions

Limited knowledge is available regarding how curcumin interacts with commonly used regimens for CLL. An in vitro study of CLL cells taken from patient donors studied curcumin (at 1 μM) with fludarabine, dexamethasone, vincristine, and rolipram. Curcumin had no effect or a subadditive effect when combined with fludarabine (3 patients, no effect; 2 patients, subadditive) and dexamethasone (3 patients, no effect; 2 patients, subadditive). When combined with vincristine or rolipram, curcumin had a supra-additive (vincristine, 4 of 5 patients; rolipram, 4 of 5 patients) or an additive effect (rolipram, 1 of 5 patients).[45]

Curcumin, combined with rapamycin, has also been studied using CLL cells isolated from patients and was associated with increased caspase-9, -3, and -7 activity, decreased antiapoptotic Bcl-2 levels, and increased proapoptotic protein Bax levels.[54] At present, the role of rapamycin in CLL has not been fully elucidated. Curcumin is known to inhibit several drug metabolizing enzymes including glutathione-S-transferase, cytochrome P450, and UDP-glucuronosyltransferase.[55-58] At present, no in vivo studies have considered the potential drug toxicities.

Clinical Trials

One clinical trial has reported on curcumin use in CLL patients.[59] The trial enrolled 21 patients with significant lymphocytosis ($> 20 \times 10^9$ lymphocytes/L) and stage 0 to 1 CLL. Patients received 2000 mg of curcumin orally once daily for 6 months, and peripheral blood samples were assessed every 2 months for the response. No objective responses were noted. Four patients (20%) showed a > 20% reduction in ALC throughout the study, with 1 patient experiencing an increase in ALC while taking curcumin. All 4 patients had an increase in ALC 3 months after withdrawal of therapy. Also, all the 4 patients who benefited from treatment had an increase in their CD4 counts during therapy, and 2 patients had an increase in their CD8 and natural killer cells. This alludes to the potential immune modulating role of curcumin. Any potential side effects or toxicity were not discussed in the study.[59] Although toxicity data in CLL were not reported, a recent phase I study of curcumin for patients with colorectal cancer might help elucidate curcumin's toxicity profile.

In a phase I dose-escalation study of curcumin that included 15 patients with advanced colorectal cancer refractory to standard chemotherapy regimens, curcumin was well tolerated at all dose levels. Gastrointestinal side effects were the most common, with 2 patients experiencing diarrhea (grade 1 in 1 and grade 2 in 2) and 1 patient experiencing nausea (grade 2). Also, 4 patients had an increase in alkaline phosphatase levels (grade 1 in 2; grade 2 in 2) and lactate dehydrogenase increased > 150% of the pretreatment values in 3 patients. None of the patients had partial responses to treatment, and 2 patients exhibited stable disease using radiologic criteria.[60]

An active phase II clinical trial (ClinicalTrials.gov identifier, NCT02100423) with 36 patients is studying curcumin and vitamin D for previously untreated patients with early-stage CLL or small lymphocytic lymphoma scheduled to be completed in October 2018.[61] Other trials of solid malignancies are studying curcumin in conjunction with typical chemotherapy regimens, as a preventative in high-risk populations, to decrease the potential side effects of chemotherapy, or to establish the intratumor bioavailability oral curcumin.[48]

Toxicity

From the limited numbers of treated patients in the clinical trials, turmeric appears to be well tolerated. The most common side effects were gastrointestinal, including nausea and diarrhea. Some evidence, from a mouse model, has shown that curcumin can act as an iron chelator. Mice, in particular, those that were fed iron-deficient diets, developed iron-deficiency anemia with decreased iron levels in the liver, bone marrow, and spleen. This could be of clinical importance, because anemia can be an important complication of CLL.[62]

Study Limitations

In vitro studies of curcumin have shown that a mean serum level of 5.5 μM and a 24- to 48-hour period of constant exposure was required to induce apoptosis of CLL cells.[45] Owing to its low bioavailability, poor absorption, low water solubility, and rapid metabolism by hepatic and intestinal glucuronidation, large oral doses of curcumin are required to achieve even transient serum levels of 1 μM.[45,47] One study of 12 healthy human volunteers consuming 10 to 12 g of curcumin found that only 1 subject had a detectable free curcumin level at any of the time points assessed (range, 0.25-72 hours).[63] Therefore, it would likely require a constant intravenous infusion to achieve a therapeutic dose of the drug or augmentation with another substance.[45] Research is underway to develop more bioavailable curcumin formulations, including tablets, powders, liposomal encapsulations, emulsions, and nanoparticles.[47,64]

Conclusion

At present, the evidence is insufficient to recommend the usage of turmeric or curcumin extracts as CLL-directed therapy. Although the treatment has very limited toxicity, no oral regimen has been shown to be tolerated and able to achieve the perceived therapeutic levels in serum.

Discussion

Oncologists must be equipped with the knowledge to educate and advise their patients about CAM. At present, CAMs, including green tea and turmeric, are not established components of accepted CLL treatment algorithms, owing to the relative lack of clinical trial data and an understanding of the potential drug interactions.

CAMs are not currently regulated as prescription medications under the US Food and Drug Administration. In the United States, the Dietary Supplement Health and Education Act of 1994 has classified herbals and supplements as "anything that supplements the diet."[65] At present, dietary supplements can be produced, sold, and marketed without demonstrating safety and efficacy such as is required for pharmaceutical agents.[65] Evidence has shown that over the counter CAMs can be adulterated or contaminated with unwanted impurities or foreign matter.[66] Herbal medicines have also been found to have inconsistencies in the levels of suspected active ingredients between different manufacturers.[65] The USP is an organization that evaluates over the counter supplements in terms of manufacturing standards, adulteration, and contamination; however, at present, supplements are not required to meet the USP standards.[41] The World Health Organization has begun a global initiative to improve the scientific standards of CAM, regulating the harvesting and manufacture of herbal medicines, and overseeing the training of farmers and CAM practitioners.[67]

Conclusion

For CAM to be adopted as a component of accepted CLL treatment, we must hold CAM to the standards of pharmaceutical agents with appropriate controlled trials and regulations for the safety of our patients. Until then, it is important that oncologists remain informed about the highly used herbal supplements to better counsel their patients. The present review did not address the use of green tea or turmeric for nonmedical purposes but the use of these substances, or their extracts, as components of oncologic treatment.

Disclosure

The authors have stated that they have no conflicts of interest.

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