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ORIGINAL ARTICLE

Taurine attenuates chemotherapy-induced nausea and vomiting in acute lymphoblastic leukemia

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Abstract Taurine has multiple physiological activities and it is decreased by chemotherapy. The purpose of our study was to evaluate the effect of oral taurine supplementation on the incidence of chemotherapy-induced nausea and vomiting in patients with acute lymphoblastic leukemia. Forty young patients aged over 16 (range: 16–23 years) suffering from acute lymphoblastic leukemia (all receiving same chemotherapy regimen) were recruited for the study at the beginning of maintenance course of their chemotherapy. The study population was randomized in a double-blind manner to receive either taurine or placebo (2 g per day orally, divided into two doses, taken 6 h after chemotherapeutic agents) for 6 months. Life quality and adverse effects including nausea and vomiting, taste and smell alterations, and weariness were assessed using a questionnaire. Data were analyzed using Pearson's Chi-square test. Of 40 participants, 32 finished the study (14 female and 18 male; mean age 19.2 ± 1.9 years). Four treatment and four placebo arm patients discontinued: one immigrated from the province, one died during the study, and six refused to continue. The results indicated that taurine-supplemented patients reported a significant ($P < 0.05$) improvement in chemotherapy-induced nausea and/or vomiting after taking taurine during study. Taurine significantly improved chemotherapy-induced taste and smell alterations ($P < 0.05$). Moreover, taurine significantly reduced weariness compared to placebo group ($P < 0.05$). This study showed that taurine co-administration decreased chemotherapy-induced nausea and vomiting during the maintenance therapy in acute lymphoblastic leukemia.

Keywords Acute lymphoblastic leukemia · Taurine · Chemotherapy-induced adverse effects · Nausea and vomiting

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Introduction

Acute lymphoblastic leukemia (ALL), a lymphoproliferative disorder, is known by rapid proliferation of cancerous lymphoid cells (Pui et al. 2004). ALL is characterized by uncontrolled production of immature lymphocytes, lymphoblasts, which are not able to fight against infections as mature lymphocytes normally do. Production of normal blood cells diminishes by disproportional increase of lymphoblasts in bone marrow so it leads to a deficiency in all types of mature blood cells circulating in peripheral blood (El-Sabagh et al. 2011). Clinical presentations of ALL include malaise, fatigue, weight loss, diminished food intake, fevers, dyspnea, angina, dizziness, lethargy, night sweats, spontaneous bleeding, joint and bone pain,

headache, nausea and/or vomiting (Larson and Anastasi 2008; Frankfurt et al. 2010).

Chemotherapy is considered as the main treatment for most types of cancer including ALL. During chemotherapy, patients may have different kinds of complications caused by the disease itself, decreasing number of peripheral blood cells or toxic adverse effects of chemotherapeutic agents (Bergkvist and Wengstrom 2006). These adverse effects vary from mild and nonspecific to life threatening and organ specific toxicities and consist of hematological, gastrointestinal, dermatological, pulmonary, neurological, cardiac, renal, hepatic and gonadal toxicities (Carr et al. 2008; Vagace and Gervasini 2011). Preventing or decreasing these side effects plays an important role in cancer chemotherapy (Reiss and Reiss 1999).

Gastrointestinal problems caused by chemotherapy include xerostomia and stomatitis, oral mucositis, nausea and vomiting, taste changes, anorexia, diarrhea, and constipation (Catane et al. 2006; Carr et al. 2008).

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common adverse effects of chemotherapy in cancer patients. The severity of CINV has a wide range, from very mild emesis to severe vomiting which may lead to malnutrition, dehydration and electrolyte or metabolic imbalances. Additionally CINV is classified into three classes: acute (occurs within the first 24 h after therapy), delayed (occurs >24 h postchemotherapy and lasts from one to seven days) and anticipatory (experiencing nausea and/or vomiting before receiving another course of chemotherapy) (Reiss and Reiss 1999). Although various antiemetic drugs, e.g., 5-HT3 receptor antagonists are widely administered to control the nausea and vomiting produced by cancer chemotherapy, CINV still remains an important clinical problem, which affects patient's quality of life and inflicts an extra economical pressure on patients and society.

Taurine (2-aminoethane sulfonic acid) is a β-amino acid that differs from other amino acids by having a sulfonic acid group instead of a carboxylic acid group. Taurine is one of the most abundant free amino acids in mammalian tissues but it is not included in proteins structure. It is known as a conditionally essential amino acid which is present in the brain, heart, liver, neutrophils, retina, and kidneys of mammals in high concentrations (Huxtable 1992; Oja and Saransaari 2007). It acts as an antioxidant, xenobiotic conjugant, osmoregulator, intracellular calcium flux regulator, bile acid conjugator, neuromodulator, cell membrane stabilizer, and also plays an important role in cell proliferation and viability (Huxtable 1992; Harada et al. 2000; No authors listed 2001; Oja and Saransaari 2007). Taurine is known to have regulatory activities in gastrointestinal tract including modulation of acid secretion and gastric motility (Huang et al. 2011); besides, it protects the gastrointestinal mucosa from the injuries (Son et al. 1996). It could also enhance the absorption of some drugs (Kim et al. 1982) and attenuates stress-induced gastrointestinal disease (Zeybek et al. 2006) and drug-induced inflammation or damage (Balasubramanian et al. 2004; Şener et al. 2005). Additionally plasma taurine concentrations decrease significantly after chemotherapy and radiation (Desai et al. 1992). Previous studies mentioned that taurine administration could decrease radiation-induced injuries (Abe et al. 1968). Therefore, taurine supplementation could be helpful in reducing chemotherapy-induced adverse effects.

The purpose of the present study was to evaluate the possible effects of taurine co-administration in prevention of chemotherapy-induced nausea and vomiting in ALL patients.

Materials and methods

Data collection

Data were collected by a medical team in an oncology clinic. As patients entered the study, baseline information was established about their perceptions of life quality and chemotherapy-associated symptoms by a questionnaire. The questionnaire included questions about the presence of each chemotherapy-associated symptom, the severity of them and whether they were getting better or worse since last visit. The same questionnaire was used and answers recorded at scheduled visits alongside their chemotherapeutic treatment.

Study design and setting

This double-blind, placebo-controlled trial study was conducted in the clinic of oncology, Shahid Ghazi hospital, Tabriz, Iran, after receiving written and signed informed consents from all patients. The study was approved by research ethics committee of Tabriz University of Medical Sciences.

Simple randomization method with an allocation ratio of 1:1 was used for this study. Patients were randomized to either placebo or taurine groups at the beginning of their maintenance chemotherapy.

Taurine (Aviforme, UK) was provided as pure powder. Both taurine and placebo were provided as 500 mg opaque capsules by the Department of Pharmaceutics, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Patients in both groups received two 500 mg capsules each time twice a day (2 g/day), 6 h after chemotherapeutical agents. This supplementation was given throughout the chemotherapy for 6 months, and responses were evaluated

by questionnaire and direct physical examination at two months intervals. Questionnaires were then evaluated based on improvement or worsening of symptoms from chemotherapy-induced toxicities, including nausea and vomiting, taste and smell alterations, and weariness.

Study population

Patients were selected from out patient chemotherapy clinic in Tabriz. Forty young patients suffering from ALL were enrolled in the trial. Patients were eligible for inclusion if they aged over 16 years. The study was open to patients being treated according to Cancer and Leukemia Group B (CALGB) 8811 chemotherapy regimen for ALL in adults. The applied regimen described by Larson et al. (1995) consisted of five courses: "the induction phase (course I) consisted of a single dose of cyclophosphamide on first day, three consecutive days of daunorubicin, weekly vincristine, biweekly subcutaneous (SC) L-asparaginase, and 3 weeks of prednisone. Early intensification (course II) included 2 months of treatment using cyclophosphamide, SC cytarabine, oral 6-mercaptopurine (6-MP), vincristine, SC L-asparaginase and also intrathecal (IT) methotrexate. In course III, the CNS prophylaxis was completed with cranial irradiation (2,400 cGy) and 5 weekly doses of IT methotrexate with daily 6-MP, followed by a maintenance period of daily oral 6-MP and weekly oral methotrexate. Course IV was a late intensification course lasting 8 weeks, followed by prolonged maintenance treatment (course V) with daily 6-MP and weekly methotrexate plus monthly pulses of vincristine and prednisone" (Larson et al. 1995).

Patients were recruited from the oncology clinic at the initiation of maintenance course of chemotherapy treatment. During the study, four patients were dismissed from each group. One patient was lost to a follow-up (because he moved out to live in another province), one patient died during the observation period; six patients initially consented and then refused to continue as a participant in our study because of the following reasons: three patients mentioned that their symptoms were getting worse, one patient chose not to continue chemotherapy, and the remaining two could not tolerate the daily dosage of taurine.

Data analysis

Statistical analysis was carried out using Statistical Package for the Social Science for Windows (SPSS, version 13.0). Patient's demographic data and the differences in chemotherapy-induced adverse effects between taurine and placebo groups were analyzed using Pearson's Chi-square test (Fisher's exact test). $P < 0.05$ was accepted to indicate statistical significance.

Results

A total of 40 ALL patients were enrolled in the study during their maintenance chemotherapy which was equally divided into taurine and placebo groups using simple randomization method. 32 patients (80 %) finished the study; from which 18 participants (56.3 %) were male and 14 participants (43.8 %) were female (ranging from 16 to 23 years, mean age 19.16 ± 1.95 years). The mean age of taurine-treated group was 19.19 ± 2.14 years while that of control group was 19.12 ± 1.82 years which were not significantly different from each other ($P > 0.05$).

Half of these patients (16 participants or 50 %) were high school students, eight participants (25 %) were unemployed, six participants (18.8 %) were studying at the university and the remaining two patients (6.2 %) were self-employed. Most of them (30 participants or 93.8 %) were single.

At the baseline point of the study, 14 participants (43.8 %) were experiencing episodes of CINV and there were no significant differences between taurine and control groups ($P > 0.05$). Figure 1 revealed the occurrences of almost similarly patterned daily CINV episode(s) experienced by participants. Compared to the placebo group, 14 taurine-supplemented patients (87.5 %) reported an improvement in CINV during whole study period (Fig. 2) and there were statistically significant differences between two study groups ($P < 0.05$).

Of all participants, 16 patients (46.9 %) reported a change in their smell sensation at the initiation of the study (seven participants or 43.8 % of taurine and eight participants or 50 % of placebo patients) but the data did not differ significantly between taurine and placebo groups ($P > 0.05$). Taurine co-administration resulted in a 37.5 % (six participants) improvement in smell changes during whole study period in comparison to the lower degrees of improvement in placebo group (Fig. 3). The difference between the improvement of smell changes in taurine and placebo-treated groups was found to be statistically significant ($P < 0.05$).

At initial point of the study, unpleasant changes in taste sensation were reported by 40.6 % (13 participants) of total patients (eight patients or 50 % of taurine and five patients or 31.3 % of placebo group) without any significant difference between placebo and taurine arm groups ($P > 0.05$). However, during the study, more than 30 % of taurine-treated patients reported an improvement in their altered taste sensation (six participants or 37.5 %, five participants or 31.3 % and six participants or 37.5 % at first, second and third visits, respectively) compared to less than 13 % of improvement reported in placebo-treated patients (two participants or 12.5 %, one participants or 6.3 % and no

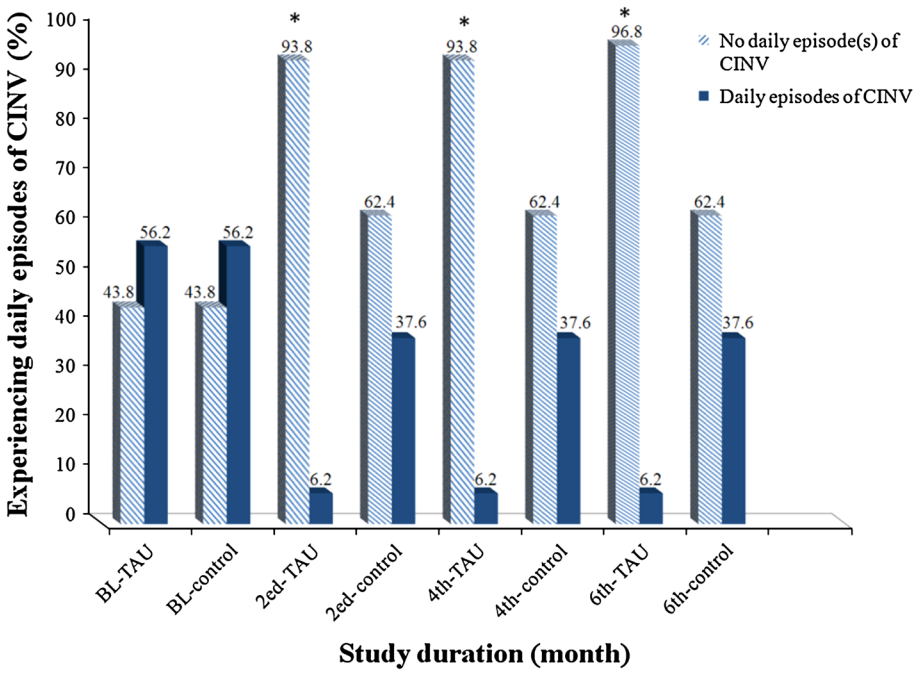

Fig. 1 The occurrence of daily CINV in ALL patients in the presence (TAU) and absence of the Taurine (control). The percentages of patients who either experienced any daily CINV or did not experience during the maintenance course of chemotherapy are plotted against the data collecting visits. *$P < 0.05$ compared with control group

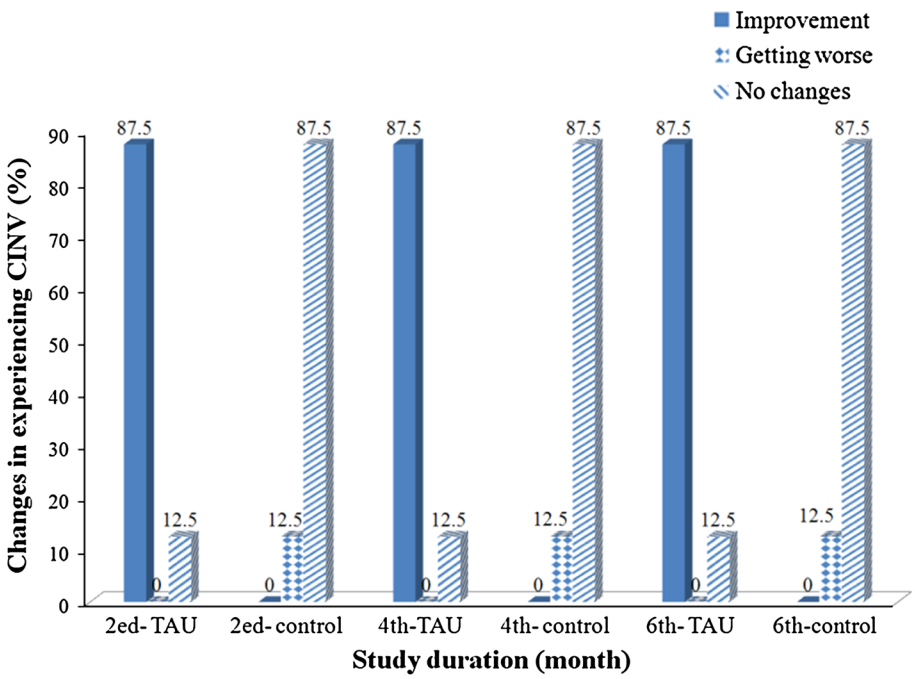

Fig. 2 The incidence of changes in daily CINV patterns in ALL patients in the presence (TAU) and absence of the Taurine (control). The percentages of patients who either experienced any change (improvement or worsening) or did not experience in daily CINV during the maintenance course of chemotherapy are plotted against the data collecting visits. *$P < 0.05$ compared with control group

participants) (Fig. 4). The differences between two study groups were statistically significant ($P < 0.05$).

Of all patients, 21 participants (65.5 %) complained of losing appetite at the beginning of the study (12 participants or 75 % of taurine and nine participants or 56.3 % of placebo groups) but the differences between two groups were not significant ($P > 0.05$).

In comparison to placebo group, a significant appetite improvement was observed in taurine-supplemented group during all visits (Fig. 5).

Moreover, 62.5 % of study population (20 participants) experienced degrees of weariness (fatigue) at the initiation of the study where there were no significant differences in both study groups ($P > 0.05$). Patients receiving taurine reported improvement in weariness rather than the chemotherapy only group, which reported 62.5 % (ten patients), 62.5 % (ten patients), and 43.8 % (seven patients) improvement at the first, second and third visits, respectively compared to 6.3, 12.5 and 6.3 % improvement in placebo group during the study. There was a significant improvement in

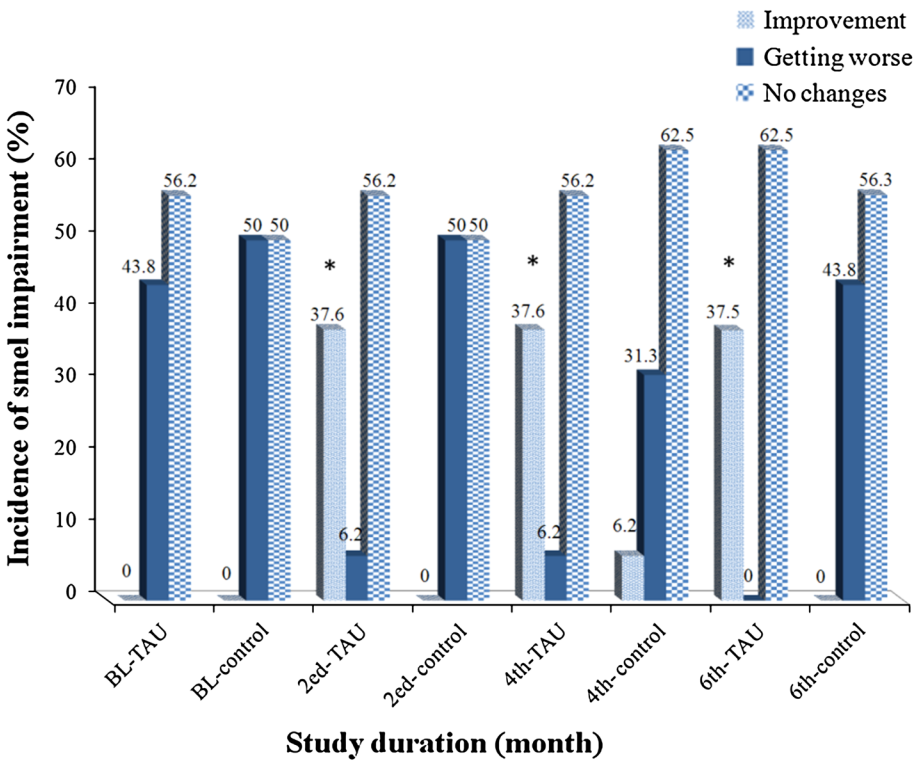

Fig. 3 The incidence of smell impairment in ALL patients in the presence (TAU) and absence of the Taurine (control). The percentages of patients who either experienced any change (improvement or worsening) or did not experience in their smell sense during the maintenance course of chemotherapy are plotted against the data collecting visits. *$P < 0.05$ compared with control group

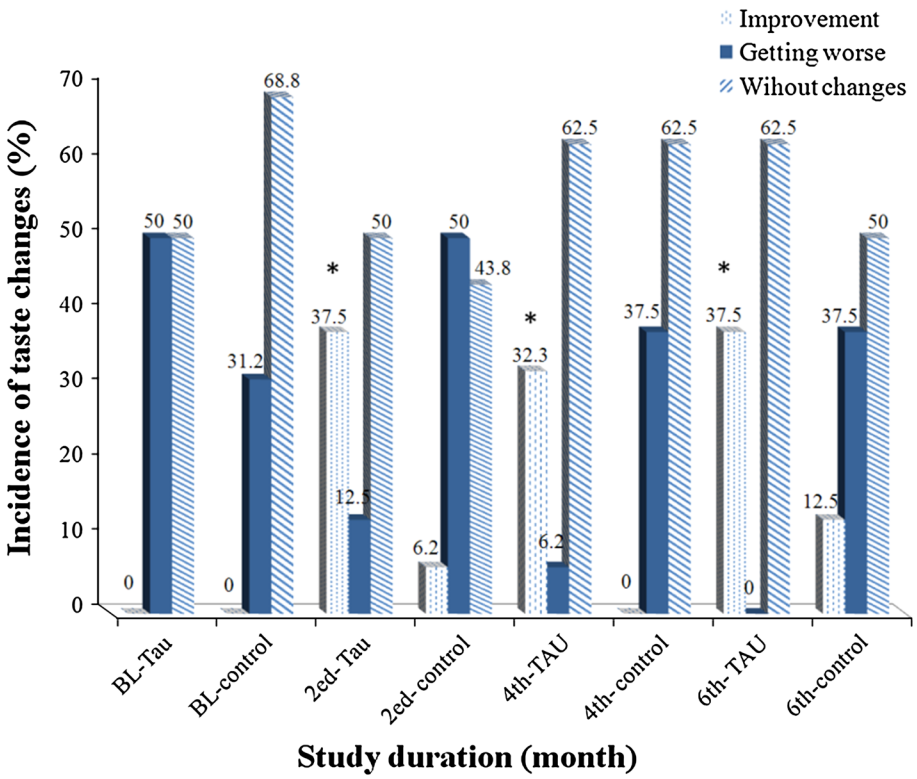

Fig. 4 The incidence of taste changes in ALL patients in the presence (TAU) and absence of the Taurine (control). The percentages of patients who either experienced any change: improvement or worsening or did not experience in their taste sense during the maintenance course of chemotherapy are plotted against the data collecting visits. *$P < 0.05$ compared with control group

feeling weary in the taurine group during all visits as compared to placebo group ($P < 0.05$).

Other chemotherapy-associated adverse effects including constipation, diarrhea, oral cavity and respiratory tract symptoms, skin lesions, musculoskeletal and neurosensory problems were also evaluated but the data were not significantly different between the taurine and placebo patients.

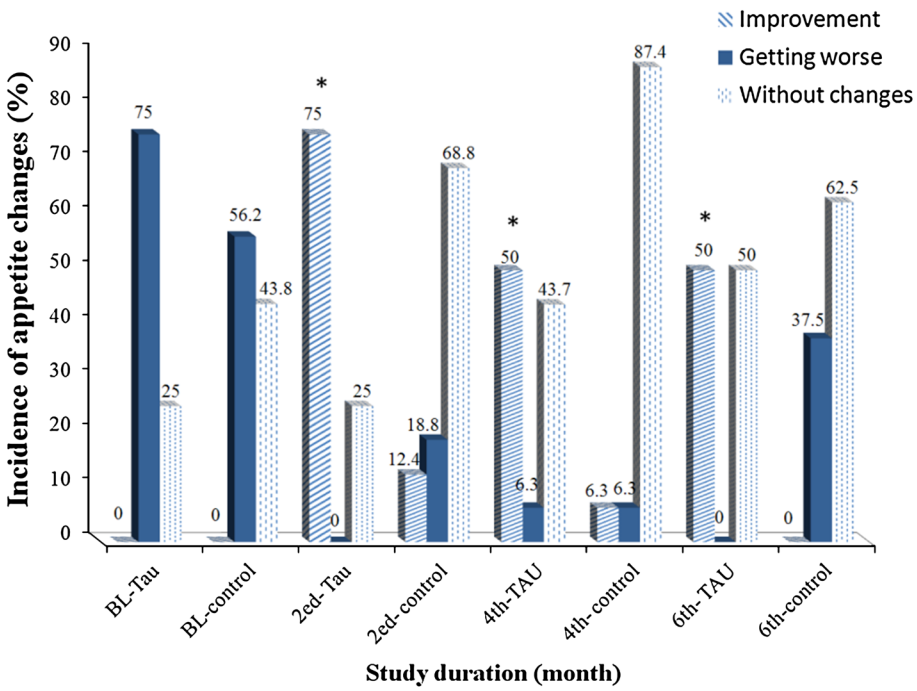

Fig. 5 The incidence of appetite changes in ALL patients in the presence (TAU) and absence of the Taurine (control). The percentages of patients who either experienced any change (improvement or worsening) or did not experience in their appeal to food during the maintenance course of chemotherapy are plotted against the data collecting visits. *$P < 0.05$ compared with control group

Discussion

In this study, we tried to estimate the effectiveness of taurine as a chemo-protective agent in ALL patients. Our findings indicated that taurine could attenuate adverse drug effects associated with chemotherapy such as nausea and vomiting, decreased appetite, taste and smell impairment and weariness. It was shown that taste and smell changes are not only measurable physiological changes but also include food preference and enjoyment (Bartoshuk 1990). So we preferred to use self-reported questionnaires as a measure of toxic effects on patients, their life quality and chemosensory perceptions.

About three decades ago chemotherapy-associated nausea and vomiting was described as the most common and fearful adverse effect of chemotherapeutic agents (Coates et al. 1983) and sometimes made patients want to postpone therapy or refuse to start a new course of chemotherapy. More recent studies showed that nausea and vomiting were still among the five most common and severe adverse effects of chemotherapy (Griffin et al. 1996) which had a negative impact on patients' life quality (Cohen et al. 2007). The exact physiological mechanisms of chemotherapy-induced nausea and emesis are not completely understood (Sanger and Andrews 2006). Studies showed that multiple areas involve in vomiting process including area postrema, vomiting center in medulla, vagal afferent pathway and the enterochromaffin cells in the gastrointestinal tract. Additionally different types of neurotransmitter receptors are taking part in vomiting process, including dopamine, serotonin and P-substance receptors (Bayo et al. 2012). Our study demonstrated that taurine could significantly improve chemotherapy-associated nausea and vomiting. The possible mechanisms for the inhibitory effect of taurine on CINV may have resulted from its neuroprotective or inhibitory neurotransmitter actions (Okamoto et al. 1983; Wu and Prentice 2010). At the presynaptic site, taurine may inhibit voltage gated calcium channels and/or open the chloride channels and suppress the release of excitatory neurotransmitters like glutamate. It may also increase K^+ efflux to decrease the postsynaptic depolarization (Wu and Prentice 2010; Banerjee et al. 2013). According to Okamoto et al. (1983) and Wu et al. (2010) taurine could act as an inhibitory neurotransmitter therefore taurine supplementation could lead to a reduction in CINV; likewise, in our study, the co-administration of taurine along with chemotherapeutical agents significantly decreased nausea and vomiting in taurine group.

Flavor is the sensory impression of foods and is determined mainly by the combination of taste, smell and oral somatosensory sensations. Patients receiving chemotherapeutic agents experience degrees of taste and smell alterations (Zlotolow and Berger 2002; Bernhardson et al. 2009). Olfactory and gustatory alterations have a negative impact on patients' quality of life (Epstein et al. 2002). The present study showed a significant improvement in taste and smell impairments in the taurine group compared to the control group. Previous studies showed the inhibitory action of taurine in olfactory bulb by decreasing their excitability (Belluzzi et al. 2004) and also by modulating release of

γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, or by directly acting on GABA receptors, to decrease mitral cells spontaneous activation, while keeping their response to odor intact (Puopolo et al. 1998; Chaput et al. 2004). Patients receiving chemotherapeutic drugs reported hypergeusia (abnormal acuity of the taste), disgeusia (taste change) or a bitter or metallic taste sensation (Ravasco 2005). It was demonstrated that GABA acts as an inhibitory neurotransmitter in taste buds (Obata et al. 1997) and as mentioned above; taurine acts as an agonist for GABA receptors (Schuller-Levis et al. 1994) therefore, taurine may play a role in decreasing taste sensation and improving hypergeusia in our study. Moreover, it was confirmed that GABA could act as a bitterness inhibitor because of its neurotransmitter activity and its receptor was also suggested as a signal transducer or modulator between taste receptor cells and output cells. Moreover, it was shown that taurine could reduce bitter taste (Ley 2008). Therefore taurine, as a GABA agonist, may be helpful in patients experiencing a bitter taste during their chemotherapy treatment.

We found that compared to the control group, taurine supplementation significantly improved appetite (Comeau et al. 2001). It was reported that taste and smell alterations have a negative impact on food intake (Schiffman and Graham 2000), additionally both of them are closely involved in full sensation of flavor (Ravasco 2005) therefore, amendment of taste and smell alterations may improve food appeal in cancer patients.

The possible mechanisms of cancer-related fatigue consist of dysregulation of serotonin (5-HT) neurotransmitter (elevation of 5-HT levels in the brain and/or upregulation of 5-HT receptors), alterations in muscle metabolism, decreased cellular adenosine triphosphate (ATP) levels and proinflammatory cytokines dysregulation including elevated levels of tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6). Prior studies suggested that there was a feedback loop between TNF-α and 5-HT levels in CNS, in which TNF-α could cause an elevation in 5-HT release into the synaptic space, conversely, 5-HT could decrease the production of TNF-α. As mentioned in the literature review, cancer treatment could disregulate the feedback loop (Ryan et al. 2007) and bring about ATP depletion as well as an elevation in skeletal muscle metabolism which resulted in fatigue. At the same time, it was demonstrated that taurine supplementation could inhibit the production of TNF-α (via chlorotaurine formation) (Schuller-Levis et al. 1994) and increase the production of ATP and cytoplasmic ATP levels (Han et al. 2004). Previous studies demonstrated that taurine deficiency was accompanied by exhaustion and muscular fatigue (Perry et al. 1975; Hamilton et al. 2006). Furthermore, it was reported that taurine supplementation can decrease the accumulation of lactate in the muscles after exercise (Manabe et al. 2003). Other studies showed that oral taurine had an anti-fatigue ability, enhanced or maintained exercise ability and prolonged the duration of exercise to exhaustion time (Wei et al. 2001; Yatabe et al. 2003, 2009). In line with these studies, we found out that experiencing weariness was significantly decreased in taurine-treated patients compared to the placebo group.

Conclusion

The present study successfully demonstrated that taurine can decrease the incidence of chemotherapy-induced nausea and vomiting and attenuate chemotherapy-induced taste and smell impairment and fatigue in ALL patients during their maintenance chemotherapy. Furthermore taurine supplementation could lead to a more tolerable chemotherapeutic treatment for the patients.

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Conflict of interest There is no conflict of interest.

Informed consent The authors state that all patients gave their informed consent prior to their inclusion in the study.

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