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Integr Cancer Ther 2009; 8; 409 originally published online Nov 25, 2009;
DOI: 10.1177/1534735409348865

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Integrative Cancer Therapies
8(4) 409–415
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DOI: 10.1177/1534735409348865
<http://ict.sagepub.com>


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Abstract

L-Glutamine (L-GLN) is considered a nonessential amino acid that has a variety of applications in naturopathic medicine. It has been postulated that in the critically ill patient, GLN becomes an essential amino acid for recovery, restoration, and repair at a cellular level. Mucositis is an intestinal mucosal damage of the gastrointestinal tract—mouth, throat, stomach, intestines, rectum, and anus—that is caused directly by chemotherapies and radiotherapies. Cancer cachexia is a significant biochemical event, which is characterized by weight loss, fatigue, and indicative of depletion of skeletal muscle GLN—a hypercatabolic state. There has been some question as to the use of GLN in this patient population because of its role as a preferred energy source not only for enterocytes and lymphocytes but for malignant cells as well. This article will address the questions of safety, efficacy, dosing, and toxicity of GLN used as an integrative therapeutic in ongoing integrative cancer treatment.

Keywords

integrative cancer treatment, mucositis, stomatitis, cachexia, diarrhea

Background

Glutamine (GLN) was first isolated from beets in 1883 by Schulze and Boshard; in 1932, Damodaran extracted GLN from a protein hydrolysate derived from wheat gluten.¹ GLN is considered a nonessential amino acid, although it has many primary biochemical roles. It is the preferred energy source for cells with rapid turnover such as lymphocytes, enterocytes, and malignant cells while also being indirectly involved in the regulation of protein synthesis. GLN is also a precursor for DNA and glutathione (GSH) synthesis. It is an essential energy source in the maintenance and restoration of the gastrointestinal (GI) tract. It also acts to protect the morphological and histological structure of the GI tract as well as to maintain the intestinal physiological structure. GLN becomes an essential amino acid in renal aminogenesis and nucleotide synthesis while acting as a regulatory substrate in protein synthesis.² In recent studies, GLN was reported to be an essential amino acid in critically ill patients. Studies suggest that it may be mandatory in patients receiving chemotherapy and radiotherapy, both of which cause intestinal mucosal damage, either stomatitis, mucositis, or enterocolitis.^{3–5} Mucositis affects the rapidly dividing mucosal cells of the GI tract—mouth, throat, stomach, intestines, and down to the rectum

and anus. These GI cells normally have a short life span of 3 to 4 days and use GLN as an oxidative fuel source. Oncological therapies can destroy these cells quickly.^{2,5,6} If these cells are not replaced right away an inflammatory process begins that creates ulcerations. Ulcerations in the mouth are called stomatitis. They are a direct effect of mucositis and generally do not start out as an infective event. Over time, however, these open lesions can become infected by opportunistic bacteria and yeast. These raw ulcerations are not limited to the buccal mucosa but are characteristic of all tissue in the GI tract.^{5–8} The patient experiences raw, open sores in the mouth and throat (stomatitis), a feeling of “sunburn” in the GI tract (mucositis), and even bowel irritation (enterocolitis), including diarrhea and/or constipation.^{5–8} This event is extremely painful and may require pain medication (lidocaine) with preventive antimicrobials and antifungals used orally until the mucosa can regenerate

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itself and the tissues recover. The major complications from mucositis are pain, infection (both of which can interfere with eating), nausea, vomiting, diarrhea and/or constipation, and less often, hemorrhage.⁵⁻⁸ Mucositis caused by chemotherapy typically begins 3 to 5 days after the start of therapy and peaks 7 to 10 days later. It may then subside or persist for weeks after the treatment is finished. Mucositis caused by radiation usually appears after the second week of treatment and may persist for weeks after the treatment is completed. All these side effects are detrimental to the cancer patient during active treatment and during the recovery stages of treatment because they not only affect the mucous membranes of the GI tract but also aggravate cachexia.⁹

In a pilot study using oral GLN to prevent chemotherapy-induced stomatitis, 12 patients received doxorubicin, 1 received etoposide, and 1 received ifosfamide, etoposide, and carboplatin. The patients were given 4 g of GLN swish and swallow twice a day, from day 1 of chemotherapy for 28 days, or for 4 days past the resolution of any postchemotherapy mucositis. Mucositis was reported to decrease in 12 of the 14 patients with GLN supplementation (median score 2A vs 0.5; $P < .001$). It was also reported that 13 out of 14 patients found that the total duration of mucositis decreased with GLN supplementation (2.7 ± 0.8 [mean \pm standard error of the mean] vs 9.9 ± 1.1 ; $P < .001$) using the CALGB (cancer and leukemia group B) criteria to measure mucositis.⁶

Biology and Biochemistry of Glutamine

GLN is regulated in the body by 2 enzymes: glutaminase and GLN synthetase. Glutaminase hydrolyzes GLN into ammonia and glutamate. This is essential to total body nitrogen exchange in which high glutaminase activity is characteristic of rapidly dividing cells. GLN synthetase catalyzes the synthesis of GLN from glutamate and ammonia. GLN is the primary fuel for the GI epithelium while also being essential for maintenance of the gut mucosal structure.⁴ It has a trophorestorative effect on the bowel mucosa where uptake and metabolism of the amino acid occurs. When the body is under the influence of stressors, which increase the metabolic demands of the body, GLN is extracted from the skeletal muscle and released into circulation. Therefore, during times of catabolic stress, additional GLN is released into the system from skeletal muscle. During these periods of increased metabolic stress, intracellular GLN is reduced by 50%.⁵ Normal dietary intake of GLN is approximately 1 g/d. Patients with malignant tumors have reductions in plasma GLN.¹⁰ It is not fully understood why this significant reduction in GLN occurs; speculation is that it may be related to reduced muscle mass, conversion of glutamate to GLN by muscle or tumor uptake,

and decreased oral GLN intake. The effect of GLN on malignant tumor growth has been studied extensively.³ Yoshida et al¹¹ showed that GLN is taken up by the growing tumor, and the decrease in GLN in the plasma of the patient may cause cancer cachexia. Because GLN is taken from the skeletal muscle by the growing cancer and trapped by the tumor, it is important to determine whether GLN is safe to use integratively in cancer patients.

Animal and Human Models Supporting the Use of GLN Supplementation in Cancer Patients

The issue of supplementation in cancer patients is specifically related to the question of whether the cancerous tumor will take up supplemented GLN and use it as a potential growth enhancer. Klimberg and colleagues^{12,13} showed that GLN supplementation does not enhance DNA uptake in the tumor, concluding that supplemented GLN is used in non-tumor tissues such as the muscles, gut mucosa, and lymphocytes. Rouse et al⁹ examined the hypothesis that supplemental oral GLN would increase the therapeutic index of methotrexate (MTX) by improving host tolerance through altering GSH metabolism. The researchers examined the effects of oral GLN on tumor and host GSH metabolism and response to MTX. Thirty-six, 300-g Fischer 344 rats were implanted with fibrosarcomas. On day 21 after implantation, rats randomly received either 1 g/kg/d of GLN or glycine (GLY) by gavage. On day 23, after feeding for 2 days, the rats were randomized into 4 groups receiving an intraperitoneal injection of MTX (20 mg/kg) or saline (controls [CON]) as follows: GLN + MTX, GLY + MTX, GLN-CON, GLY-CON. On day 24, the rats were killed. Arterial GLN concentration, tumor volume, kidney and gut glutaminase activity, and GSH content (tumor, heart, gut, liver, muscle, kidney, and lung) were determined. The results suggested that GLN-enriched diets decreased tumor GSH (2.38 ± 0.17 in GLN + MTX vs 2.92 ± 0.20 in GLY + MTX; $P < .05$). Additionally, whereas tumor GSH was reduced, host normal tissue GLN stores were increased or maintained (in the gut, 2.60 ± 0.28 in GLN + MTX vs 1.93 ± 0.18 in GLY + MTX; $P < .05$). It has been noted that depressed GSH levels in tumor cells increases their susceptibility to chemotherapy. This study also found that significantly decreased GSH content in tumor cells in the GLN + MTX group correlated with enhanced tumor shrinkage (-0.8 ± 1.0 mL in GLN + MTX vs $+9.5 \pm 2.0$ mL in GLY + MTX; $P < .05$). These data suggested that oral GLN supplementation would enhance the selectivity of antitumor drugs by protecting normal tissues from them and sensitizing tumor cells to chemotherapy treatment-related tissue injury.⁹

The question as to whether the tumor cells would use GLN to protect themselves from chemotherapies and radiotherapies was thus answered. Researchers also showed that not only does GLN keep the healthy cells free from treatment side effects, but it may also enhance the tumor cells' susceptibility to chemotherapy. Other studies have also shown that GLN does not augment tumor growth; rather, tumor growth is counterbalanced by support of host GLN stores, GSH production, and increased immune function via natural killer (NK) cell activity^{9,14}:

Glutamine by decreasing intracellular levels of GSH in tumor cells, makes tumor cells more sensitive to radiation and chemotherapy. At the same time GLN restores the depressed levels of GSH in normal host tissues, thereby improving the overall host well being and resulting in decreased morbidity and mortality associated with cancer and its treatment. Thus, GLN supplementation effectively increases the therapeutic index of radiation and chemotherapy.¹² (p. 423)

It appears that supplementation with GLN does not increase tumor growth, as one might logically deduce; instead, tumor growth is counterbalanced by support of the system's GLN stores, GSH production, and increased immune function.⁷

Immune System Effects of GLN

Upregulation of the immune system is primarily carried out by the lymphocytes. The lymphocytes use GLN as a primary fuel source. NK cells make up one fraction of the lymphocytes. The optimal function of the NK cells depends on adequate supplies of GLN and GSH. *In vivo* evidence has documented increased NK cell activity with supplemental GLN.⁵ In a previous study by Klimberg et al,¹³ researchers showed that reduced NK activity observed in tumor-bearing hosts was associated with high levels of prostaglandin produced by monocytes *in vitro*. Previously, the researchers demonstrated a dependence of NK cell activity on GLN levels *in vitro* and *in vivo*. It was also found that GSH was antagonistic to prostaglandin E₂ (PGE₂) synthesis. The researchers hypothesized that GLN, through increased GSH production, would lead to decreased PGE₂ synthesis and upregulation of NK cytotoxic activity. Using a rat breast cancer model, 344 rats were pair-fed chow and gavaged with 1g/kg/d GLN (n = 9) or an isonitrogenous amount of Freamine (n = 9). After 7 weeks, the rats were killed. Tumors were measured, weighed, and analyzed for tumor morphometrics. Spleens were also removed, and lymphocytes were isolated and assayed for NK-cell activity. Blood GLN, GSH, and PGE₂ concentrations were also measured. Over the 7-week period, the tumor growth in the GLN-treated group was decreased by 40%, with an

associated 2.5-fold greater NK activity. This correlated with a 25% rise in GSH concentration and a proportional decrease in PGE₂ synthesis. The conclusion from this study was that oral GLN supplementation results in increased NK activity and decreased tumor growth. This activity is probably related to suppression of PGE₂ synthesis and improved NK activity, resulting in decreased tumor growth in the tumor-bearing host, associated with GSH-mediated suppression of PGE₂ synthesis.¹³ Therefore, GLN augmentation has therapeutic effects against cancer cells relating to host defenses and ability to tolerate chemotherapy regimens as well as prevention of mucositis.

Clinical investigations and animal studies have shown that supplementation with GLN may protect the GI tract from both radiation and chemotherapy and also heal it.¹⁵ GLN has an anabolic effect and is used as a major fuel source by epithelial cells lining the GI tract.^{6,15} The gut can be considered as a nitrogen-processing organ in the metabolic response to illness, with the GI tract using GLN as a respiratory fuel.⁷ GLN is the dominant amino acid in the plasma and whole blood of the body and an essential nutrient for rapidly dividing cells as well as a major source for intestinal epithelium.⁸ The digestive tract's immune system is often referred to as gut-associated lymphoid tissue (GALT) and works to protect the body from invasion. GALT is an example of mucosa-associated lymphoid tissue. GALT is associated with the gut, including the tonsils, Peyer's patches, lamina propria of the GI tract, and the appendix. Gut mucosal injury from radiation and chemotherapy also affects the GALT immune function, and GLN also acts as a substrate for this immune system function, thus, enhancing the immune system's function. GLN modulates the immune function while promoting faster intestinal healing after chemotherapy.¹⁶ Studies have shown that oral supplementation of GLN is not only efficacious in the cancer patient population but also devoid of toxic side effects.^{6,8}

Cancer Cachexia Prevention and Treatment With Glutamine

Although under homeostatic conditions GLN is not considered an essential amino acid, during times of catabolism, the GLN synthesis rate cannot keep up with the higher requirements.^{1,3} Tumor growth is inversely related to host GLN stores, and cancer cachexia is marked by massive host skeletal GLN depletion.^{5,12} GLN depletion has been found to occur after trauma or sepsis because of GLN consumption by lymphocytes and enterocytes in enhanced catabolic states.^{11,12} Yoshida et al found that the rate of GLN oxidation increased in septic rats and that GLN supplementation improved protein metabolism by decreasing the protein breakdown rate and increasing the protein synthesis rate in skeletal muscle and gut mucosa. Thus, some researchers and clinicians alike

have begun to view GLN as an essential amino acid during times of stress to the system. It has been suggested that 15 to 35 g/d of supplemental GLN are needed to preserve musculoskeletal GLN, maintain gut integrity, and provide fuel for cells during stressful events.¹⁷ Cancer cachexia is a significant biochemical event, a hypercatabolic state that is characterized by weight loss and fatigue and is indicative of depletion of skeletal muscle GLN. Patients in this hypercatabolic state cannot synthesize adequate amounts of GLN from endogenous sources.² Cachectic patients given GLN added to enteral formulas had improved anthropometric and immunological measurements as well as plasma protein levels, which reached statistical significance postoperatively in the GLN-treated group.²

Normal tissue damage from radiation and or chemotherapy, especially in the GI tract, influences the presence of adequate GLN stores in the tissues and can also contribute to cachexia.^{4,7,18} A by-product of GLN metabolism is GSH, which protects against oxidative injury. The gut is the major site of GSH production. GSH levels in tumor cells are 5 to 50 times higher than those in noncancerous cells.¹⁹ In normal tissues, toxicity secondary to radiation and chemotherapy is created when the GSH stores are depleted—an effect that can be reversed by supplementation with oral GLN.^{4,9,20-22} GLN supplementation seems to decrease intratumoral GSH stores while increasing normal cell stores, as previously described in both animal and human studies. This suggests that GLN may enhance the selectivity of anti-tumor drugs and radiotherapies by sensitizing the tumor cells to the oncological therapeutic agents while protecting normal cells in healthy tissues.^{4,9,20-22}

Diarrhea is a direct effect of enterocolitis or damage to intestinal epithelium by chemotherapeutics and radiation therapies. Diarrhea adds proportionately to cancer cachexia malnutrition in patients during chemotherapy and radiation treatment. These cancer treatment strategies result in a denuded mucosa with an increased permeability, which is unable to absorb fluid⁴ causing the profuse diarrhea associated with cancer treatment. Human studies have shown some favorable results for the use of GLN in the control of diarrhea associated with different chemotherapies and radiotherapies.²²⁻²⁴ In a pediatric study, 11 children with acute myelogenous leukemia undergoing chemotherapy with supplemented GLN (6 g, 3 times a day) were compared with 22 children not given GLN. The GLN-supplemented children showed a shorter duration of diarrhea with lesser incidence of >6 stools per day.²³

Mucositis Prevention and Treatment With Glutamine

Cytotoxic chemotherapies and radiotherapies are most effective against rapidly dividing cells. As a consequence of

this mechanism, these conventional treatment interventions may also damage host tissues that contain rapidly dividing cells. The cells of the GI tract are the most rapidly proliferating cells in the human body. These intestinal cells absorb large amounts of GLN and metabolize nearly all the absorbed dietary GLN in addition to extracting circulating GLN from other tissues. Mucositis—that is, inflammation of the mucous membranes lining the digestive tract from the mouth to the anus—is a common toxic side effect of cancer chemotherapy and radiotherapy,^{6,7,23-27} and it can involve any part of the digestive tract.²⁸

As mentioned earlier, it was found in a pilot study⁶ that GLN can significantly decrease the severity and duration of mucositis/stomatitis induced by chemotherapy and radiation treatments, which is a significant side effect in this patient population and an important cause of increased morbidity in patients being treated for cancer.⁶ Anderson et al⁷ used oral GLN in a randomized, double blind, crossover trial in stomatitis-affected cancer patients receiving different protocols of chemotherapy. In their study, 24 patients (16 children and 8 adults) were given GLN or placebo (GLY) suspension (2 g amino acid/M2/dose twice daily) swish and swallow on days of the first course of chemotherapy administration and for at least 14 additional days. In the randomized sequence, virtually all the patients were able to swish and swallow the amino acid suspension without difficulty. Paired data indicated significant amelioration of stomatitis when GLN was administered after chemotherapy. The duration of mouth pain was 4.5 days less with GLN supplementation as compared with placebo (Wilcoxon's signed rank test, $P = .0005$). It was also reported that the severity of oral pain was reduced when GLN was given during and after chemotherapy, and the duration of mucositis overall was decreased by 4 days.⁷

In tumor-bearing dogs receiving oral GLN for the amelioration of radiation-associated oral mucositis, it was necessary to continue the treatment for at least 1 week after the last dose of radiation to avoid development of mucositis. Therefore, the researchers recommended that GLN not only be provided during treatment but at least for 2 weeks after the completion of treatment, into the recovery period,⁷ for the amelioration of mucositis associated with chemotherapy and radiotherapy.

A systematic review article examining clinical evidence for enteral nutritional support with GLN in male and female patients older than 18 years found evidence of the efficacy of enteral nutritional supplementation enhanced with GLN. A diet enriched with GLN was found to be well tolerated, and it also improved mucositis after chemotherapy and in patients receiving autologous bone marrow transplants, resulting in improved quality of life and a reduced perception of severity of symptoms while improving immunological function by decreasing the inflammatory response, thus, lowering infectious morbidity in patients.²⁹

Dosing and Toxicity

Dosing

Small pilot clinical studies have been done with oral and parenteral GLN doses of up to 20 g/d via total parenteral nutrition,¹⁶ from 4 g taken orally twice a day⁶⁻⁸ to up to 30 g orally per day in divided doses,^{11,29} and it was found that this was not only a safe and effective treatment for mucositis and stomatitis but also had the added effect of lymphocyte recovery.^{6,8,11,16,28-32} It has been recommended by several researchers that the therapeutic dose range for GLN should be 20 to 40 g/d.^{29,30} It was found in one study by Daniele et al³¹ that 18 g of oral GLN supplementation and in another study by Jebb et al³² that 16 g/d had no beneficial effects on stomatitis. Anderson et al^{7,8} suggested that this lack of a beneficial effect may be because of treatment times. In other words, it seems that not just the dosage of GLN but also the duration of treatment with GLN and local contact of GLN with the mucous membranes are important key factors in the success of GLN treatment for mucositis/stomatitis. In a study using 16 g of GLN diluted in 150 mL of water and divided into 4 daily doses for 8 days, the authors found that there was no effect on 5-FU/foinic acid-induced mucositis; this was considered too low of a dose to be effective.³²

Conclusions from these pilot studies are that the oral dosing range in adult patients for therapeutic effect on mucous membranes should be 20 to 30 g in daily divided doses (which increases enterocyte contact), swished and swallowed, starting from the first round of conventional chemotherapy and/or radiotherapy until 2 weeks posttherapy.²⁹ The inability of lower doses to affect mucositis/stomatitis has been previously shown in pilot studies.^{8,26,28,33} The oral route of GLN administration is inexpensive and convenient. In one clinical trial with children, in addition to a suspending agent to keep GLN from settling out of solution immediately after shaking the suspension, a sucrose vehicle was used. The sweet suspension was very palatable to the young children, but adolescents and adults sometimes found this too sweet.⁷ The palatability of GLN is excellent because GLN is tasteless. Using the clinical data from these studies, the standard dose of 10 g, 3 times a day, swish and swallow, is the best application of GLN. The importance of GLN touching the tissues to be affected is a priority. The amino acid must directly touch the buccal mucosa, tongue, esophagus, GI, and so on to prevent and treat mucositis. Generally, the 10-g dose can be a little grainy, but if GLN is first mixed in a small amount of warm water and stirred well, the amino acid is more miscible. Then cool water can be added to create the solution that is to be swished and swallowed 3 times a day. The solution has no real flavor or taste and is tolerated well.

Toxicity

The safety of GLN supplementation has been studied by several researchers, and there has been no evidence of clinical toxicity with several different dosing strategies involving many different treatment protocols. In one dose response study, parameters of toxicity relating to blood nitrogen levels were monitored.²⁵ The researchers found no clinical evidence of toxicity or generation of toxic metabolites at doses up to 0.3 g/kg. Thus, even at doses higher than recommended for therapeutic effect, no toxicity was found. Okuno et al²⁵ found in their phase III clinical trial that nitrogen retention was enhanced when GLN was administered at a dose of 0.57 g/kg per day, with whole blood concentrations rising proportionately to the oral dosing and levels peaking 30 to 45 minutes after ingestion. These levels declined steadily to normal ranges from 1.5 to 6 hours in a dose-dependent fashion, giving data on the half-life of GLN in the blood.

In an animal study,¹¹ which was mentioned above, GLN supplementation was given to tumor-bearing rats. The conclusion of this study was that the tumor burden caused the depletion of GLN from skeletal muscle and gut mucosa, causing protein breakdown and weight loss. When supplemented with GLN, there was an associated decrease in whole body protein breakdown rate, thus, reducing weight loss. Furthermore, the investigators found that GSH levels in the jejunum were increased, whereas tumor synthesis, DNA synthesis of the tumor, and tumor growth were not stimulated by GLN supplementation. They also found that neither GLN nor GSH levels in the tumors were increased by GLN supplementation;¹¹ other researchers have observed similar results.^{4,5,7,13}

According to one dose-finding review article, no toxic side effects were found in any studies using oral or parenteral GLN supplementation, with ranges from 0.2 to 0.65 g of GLN/kg/d in pediatric oncology patients, with plasma GLN and ammonia comparing favorably in safety and metabolic effects.³⁴ Dosage ranges may vary depending on the status of the individual patients' liver enzymes because GLN can raise the levels of liver transaminases (AST and ALT), as seen anecdotally in clinical practice. In a human clinical study investigating GLN provision in total parenteral nutrition, Daniele et al²⁴ found that high doses (0.285 g/kg once daily for 4 weeks) were associated with the elevation of hepatic transaminases. Other studies failed to demonstrate hepatic toxicity at doses of 0.285 g/kg and 0.57 g/kg.³⁵⁻³⁷ In patients with hyperammonemia or hepatic encephalopathy, GLN supplementation may be inappropriate because intestinal GLN catabolism is responsible for about 50% of the ammonia released into the portal vein. Regarding renal disease, there are no published data contraindicating GLN supplementation in patients with renal insufficiency.²⁵

Conclusion

Biochemical analysis, in vitro and in vivo, animal and human studies along with phase I-phase II human clinical trials with pilot phase III clinical trials have shown that oral GLN is a safe and effective strategy to prevent and treat mucositis, stomatitis and cachexia^{2-6,8,11,12,15-18,20-22,25,26,29-34,38,39} (M. M. Schubert, unpublished data, 2004). Concerns about GLN being preferentially used by the cancer cells, giving a tumor-protective effect, have been addressed in the research. The results show that GLN is not taken up by the cancer but preferentially by the healthy noncancer tissues like muscles, gut mucosa, and lymphocytes.^{3-5,10,11} It has been shown that cancer growth is not only reduced by GLN but also counterbalanced by support of the lost GLN stores and GLN production in healthy cells. Immune function was also increased via the increased activity of NK cells by the suppression of the PGE2 series.^{12,13,29} Thus, GLN not only has a preventive effect against mucositis and cachexia but a therapeutic effect against cancer cells in relation to the host's defenses and ability to tolerate chemotherapy.

During times of trauma and stress to the homeobalance of the system, GLN depletion has been found to occur because of GLN consumption by lymphocytes and enterocytes in an enhanced metabolic state. Therefore, GLN has gained acceptance as an essential amino acid during times of stress to the system.^{2,3,5,6} It not only modulates the immune system's function at the gut level but also promotes faster intestinal healing, significantly decreasing the severity of mucositis/stomatitis induced by chemotherapy and radiation therapy.^{3,9,11-13} GLN may also enhance the selectivity of antitumor drugs by sensitizing the tumor cells to the oncological therapeutics while protecting normal cells in healthy tissues.^{4,9,20-22} This ability to evade chemoresistance is a very important finding to add to the strategies of integrative oncology.

Dosing ranges may vary depending on the status of the individual patients' liver enzymes because GLN can transiently raise the levels of AST and ALT.²⁴ Although there are no current data that contraindicate the use of GLN with elevated liver transaminases, the current clinical thinking is that if the AST/ALT levels are higher than 3 times the normal ranges, GLN should be used as a swish and spit, and not as a swish and swallow. Safe dosing strategies include continued monitoring of these enzyme levels for this possible effect of GLN supplementation. The general consensus for effective and safe dosing strategies ranges from 10 to 40 g/d in divided doses, usually 3 times per day, swished and swallowed for optimum local contact of GLN with the mucous membranes.^{29,30}

Acknowledgments

The author would like to acknowledge several outstanding physicians and researchers who helped with the research efforts for this

article: Drs Ivette P. Farmer, Christine Girard, Petra J. Ketterl, and Michelle Qaquadah, and Leslie Johnson, MS. The author would also like to acknowledge the Cancer Treatment Centers of America (CTCA) for the foresight to allocate time, effort, and resources toward the continual research in the fight against cancer. Although the author is not affiliated with CTCA, many of the aforementioned physicians and researchers are. The author would also like to acknowledge Aimee Fontaine for her editorial help with this review article.

Declaration of Conflicting Interests

The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author received no financial support for the research and/or authorship of this article.

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