

# Oral Glutamine in Preventing Treatment-Related Mucositis in Adult Patients With Cancer: A Systematic Review

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## Abstract

**Background:** Breakdown of the mucosal barrier resulting in mucositis is a common adverse event in patients with cancer receiving chemotherapy and radiation. Many studies have evaluated the use of oral glutamine to prevent mucositis in these settings, but current guidelines make no recommendations with regard to its use. Our objective was to systematically review the evidence for the use of oral glutamine in preventing mucositis in adult patients with cancer undergoing chemotherapy and/or radiation. **Materials and Methods:** A systematic search of English-language literature was done via MEDLINE using the search terms *glutamine*, *cancer*, and *mucositis* or *esophagitis* or *stomatitis*. Fifteen studies conducted in adult patients with cancer receiving chemotherapy and/or radiation comparing single-agent oral glutamine with control were identified. **Results:** Oral glutamine was shown to be effective in 11 of the 15 studies included in the systematic review. It significantly reduced the incidence of grade 2, 3, or 4 mucositis and/or reduced weight loss as well as the duration, time of onset, and/or maximum grade of mucositis. The most common dosing regimen was 30 g/d in 3 divided doses, with other regimens ranging from 7.5–24 g/d. Rates of nausea, vomiting, dry mouth, and anorexia were similar in the glutamine and control groups. **Conclusion:** In summary, the favorable efficacy and low toxicity of oral glutamine observed in clinical trials we reviewed provide a strong rationale for large randomized placebo-controlled studies to further evaluate its efficacy in preventing mucositis in patients with cancer receiving chemotherapy and/or radiation. (*Nutr Clin Pract.* 2016;31:171-179)

## Keywords

glutamine; mucositis; esophagitis; stomatitis; cancer; chemotherapy; radiation

Mucositis is characterized by painful inflammation and ulceration of the mucous membranes lining the digestive tract and is a frequent adverse complication of chemotherapy, radiotherapy, or even targeted anticancer therapy.<sup>1,2</sup> It severely affects the clinical outcomes and quality of life of patients with cancer.<sup>1-4</sup> Adverse outcomes related to mucositis include delays in therapy, reduction in dose intensity, nutrition compromise, and increased risk for infection.<sup>5-8</sup> Depending on the type of cancer, treatment modality (chemotherapy vs radiation), types of chemotherapy, and dose intensity, 10%–100% of patients with cancer are affected by this complication.<sup>2,9</sup> Treatment delays and dose reductions are common consequences of severe mucositis during anticancer therapy, reported in up to 35% and 60% of patients, respectively.<sup>10</sup>

The high morbidity associated with mucositis warrants clinical investigation of strategies to prevent this toxicity. Although oral hygiene and cryotherapy are generally recommended to prevent mucositis and reduce its severity, this does not work for all patients as they work best when used with chemotherapy with short half-lives.<sup>11,12</sup> Two pharmacological agents are recommended for the prevention of mucositis secondary to cancer therapy by the 2014 Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) clinical practice guidelines.<sup>13</sup> The first agent, recombinant human keratinocyte growth factor 1 (KGF-1/palifermin), is

recommended in patients with hematological malignancies receiving high-dose chemotherapy and total-body irradiation prior to autologous stem cell transplantation. The second agent, benzydamine mouthwash, is recommended in patients with head and neck cancer receiving moderate-dose radiation therapy without concomitant chemotherapy. The guideline also suggests that zinc supplements administered orally may be of benefit in the prevention of oral mucositis in patients with oral cancer receiving radiation therapy or chemoradiation.

In the past 2 decades, oral glutamine has been investigated in clinical studies to prevent oral and esophageal mucositis related to chemotherapy and radiation therapy. Based on

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some of the recent studies, the recommendation for the use of oral glutamine to prevent oral mucositis was revised in the 2013 MASCC/ISOO guidelines to indicate *no guideline possible* due to inadequate and/or conflicting evidence.<sup>14</sup> This was a significant change from their previous 2007 MASCC/ISOO guidelines, which stated that systemic glutamine should not be used for the prevention of gastrointestinal (GI) mucositis because of severe adverse effects<sup>11</sup> and the 2011 Cochrane Collaboration review,<sup>15</sup> which determined that there was no evidence to support the use of oral glutamine. The recommendation for not using systemic glutamine specifically referred to a study by Pytlik et al<sup>16</sup> investigating intravenous (IV) glutamine, which reported increased oral mucositis and increased disease recurrence after stem cell transplantation with a nonsignificant increase in mortality. In addition to the adverse effects seen in this study, IV glutamine is only available as a compounded product in the United States. IV glutamine must be compounded from a nonsterile powder, classifying it as a high-risk compound according to United States Pharmacopeia (USP) 797, which may increase the risk of infection in immunosuppressed patients.<sup>17</sup> Therefore, oral glutamine may be a more appropriate dosage form to be used for the prevention of mucositis in patients with cancer. In this review, we systematically evaluate the published evidence for the use of oral glutamine for the prevention of mucositis in adult patients with cancer undergoing chemotherapy and/or radiation.

## Methods

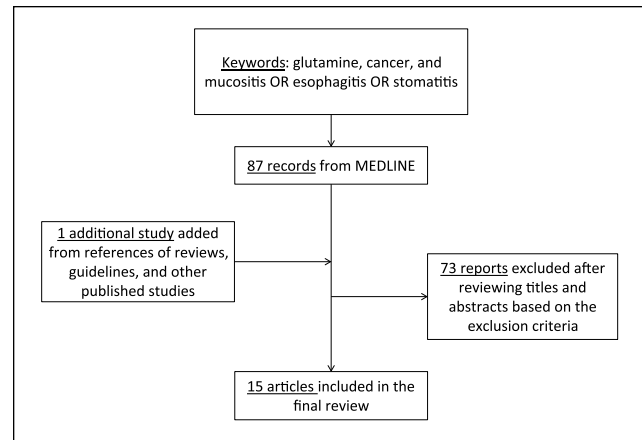
This review was performed according to the standards described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.<sup>18</sup>

### Literature Search Strategy

A systematic search of the literature via MEDLINE was done with the terms *glutamine*, *cancer*, and *mucositis* or *esophagitis* or *stomatitis*. The search was conducted on July 30, 2015. Reports were limited to English-language studies, with no limitation on publication dates. References from review articles on related topics, MASCC/ISOO guidelines,<sup>13,14</sup> and published studies included for our systematic review (as described below) were also searched for additional studies.

### Study Selection Criteria

The reports were selected after the abstracts were reviewed for the exclusion criteria, which were non-English publications, pediatric patients, use of glutamine as a treatment regimen (not prevention) for mucositis, combining glutamine with other supplements, swish-and-spit regimens, reports of nonoral glutamine products, lack of a control arm for comparison, review articles or guidelines, and nonhuman studies. Both prospective and retrospective studies were included, and only studies



**Figure 1.** Flow chart of the literature review.

evaluating the use of oral glutamine for prevention of mucositis were included.

## Data Collection

From each study, we recorded the following information: study type (prospective or retrospective), cancer type, anticancer treatment modality (ie, chemotherapy and/or radiation), number of patients for glutamine and control arms, type of control (placebo, best supportive care, etc), mucositis assessment tool, rate and severity of mucositis, and adverse events. Descriptive analysis was conducted for all the identified studies due to the high heterogeneity between patient populations and study designs.

## Results

### Study Characteristics

The systematic literature search identified 87 records (Figure 1). Seventy-three reports were excluded after reviewing titles and abstracts for the inclusion/exclusion criteria, and one study was added from references of other included studies. Fifteen published studies totaling 1171 patients were included in the final analysis. An overview of the included studies is presented in Table 1. The cancer type was different in various studies: 4 studies in lung cancer,<sup>7,19-21</sup> 3 in breast cancer,<sup>5,22,23</sup> 3 in head and neck cancer,<sup>24-26</sup> 1 with GI cancers,<sup>27</sup> 1 with hematologic malignancies,<sup>28</sup> 1 with multiple solid tumors,<sup>29</sup> 1 with various types of cancers,<sup>30</sup> and 1 study without a defined cancer type.<sup>31</sup> Ten articles were prospective,<sup>5,21,23-25,27-31</sup> and 5 were retrospective studies.<sup>7,19,20,22,26</sup> Anticancer treatment modality included chemotherapy only,<sup>5,22,23,27,29-31</sup> radiation only,<sup>19,24,28</sup> and their combination.<sup>7,20,21,25,26</sup> Ten studies evaluated oral mucositis (stomatitis) only,<sup>5,22-25,27-31</sup> 4 studied esophageal mucositis only,<sup>7,19-21</sup> and 1 evaluated both.<sup>26</sup> Three of the trials were designed as crossover studies,<sup>5,27,30</sup> while the remaining 12 used a parallel group design.<sup>7,19-26,28,29,31</sup> The smallest study evaluated 21 patients,<sup>22</sup> and the largest evaluated 326 patients.<sup>5</sup>

**Table 1.** Studies Evaluating the Efficacy of Glutamine in Preventing Mucositis in Patients With Cancer Receiving Chemotherapy and/or Radiation.

Reference	Year	Study Type (N)	Cancer Type	Chemo	XRT	Oral Glutamine		Control	Treatment Duration			Mucositis Assessment Tool	Glutamine Efficacy <sup>a</sup>
						Dose, g	Regimen		Start	End	End		
Choi et al <sup>29</sup>	2007	P (51) <sup>b</sup>	Advanced solid tumors	5-FU/leucovorin	No	10	PO TID	BSC	3 d before chemo	15 d later	CTCAE	Yes	
Peterson et al <sup>5</sup>	2007	P (326)	Breast cancer	Anthracycline based	No	2.5	S&S TID	Placebo	First d of chemo	Various <sup>c</sup>	WHO and OMAS	Yes	
Vidal-Casariago et al <sup>26</sup>	2013	R (127)	Head, neck, chest cancer	Yes	Yes	30	PO QD	BSC	Undefined	Undefined	WHO	Yes	
Chattopadhyay et al <sup>24</sup>	2014	P (70)	Head and neck cancer	No	Yes	10	S&S on XRT days	BSC	First d of XRT	On last d of XRT	WHO	Yes	
Topkan et al <sup>19</sup>	2009	R (41)	NSCLC	No	Yes	10	PO Q8H	BSC	1 wk before	2 wk after XRT	RTOG	Yes	
Topkan et al <sup>7</sup>	2012	R (104)	NSCLC	Yes	Yes	10	PO Q8H	BSC	1 wk before	2 wk after XRT	RTOG	Yes	
Tutanc et al <sup>20</sup>	2013	R (46)	Lung cancer	Yes	Yes	10	PO Q8H	BSC	First d of XRT	3 wk after XRT	RTOG	Yes	
Okuno et al <sup>31</sup>	1999	P (134) <sup>b</sup>	Undefined	5-FU based	No	4	S&S BID	Placebo	First d of chemo	14 d later	NCCTG	No	
Cockerham et al <sup>22</sup>	2000	R (21)	Metastatic breast cancer (HSCT)	Paclitaxel and melphalan	No	4	S&S Q4H	BSC	First d of chemo	No mucositis or patient discharge	CTC	Yes	
Coghlin Dickson et al <sup>28</sup>	2000	P (58)	Hematologic (HSCT)	No	Yes	10	PO TID	Placebo	First d of preparative regimen	28 d posttransplant or patient discharge	Stanford University Hospital BMT toxicity	No	
Jebb et al <sup>27</sup>	1994	P (34)	Advanced GI cancers	5-FU/leucovorin	No	4	S&S QID	Placebo	1 d before chemo	8 d later	WHO	No	
Skubitz et al <sup>30</sup>	1996	P (28)	Various	Yes	No	4	S&S BID	BSC	First d of chemo	4 d after no mucositis or 28 d later	Modified CALGB	Yes	
Gul et al <sup>21</sup>	2015	P (32)	Lung cancer	Yes	Yes	10	PO Q8H	BSC	7 d before XRT	14 d later	RTOG	Yes	
Tsujimoto et al <sup>25</sup>	2015	P (40)	Head and neck cancer	Yes	Yes	10	PO TID	Placebo	First d of XRT	Last d of XRT	CTCAE	Yes	
Li et al <sup>23</sup>	2006	P (59)	Breast	CEF	No	10	PO TID	Placebo	First d of chemo	12 d later	CTCAE	No	

5-FU, 5-fluorouracil; BID, twice daily; BMT, bone marrow transplant; BSC, best supportive care (oral hygiene); CALGB, Cancer and Leukemia Group B; CEF, cyclophosphamide, epirubicin, and fluorouracil; CTC, Common Toxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; NCCTG, North Central Cancer Treatment Group; NSCLC, non-small cell lung cancer; OMAS, Oral Mucositis Assessment Scale; P, prospective; PO, by mouth; Q4H, every 4 hours; Q8H, every 8 hours; QD, once daily; QID, 4 times daily; R, retrospective; RTOG, Radiation Therapy Oncology Group; S&S, swish and swallow; TID, 3 times daily; WHO, World Health Organization; XRT, radiation therapy.

<sup>a</sup>Based on a significant reduction in the maximum grade, duration, and/or time of onset of mucositis evident in the glutamine group summarized in Table 3 and/or 4 and/or based on the author's conclusion.

<sup>b</sup>Cryotherapy given during chemotherapy treatment to all patients.

<sup>c</sup>Glutamine was continued for 14 days after the last dose of chemotherapy in patients who did not develop oral mucositis (OM) or until 5 days after the resolution of OM for patients who experienced OM or to the end of the treatment cycle.

**Table 2.** Assessment Tools for Mucositis Severity.

Tool	Grade 1	Grade 2		Grade 3	Grade 4
		2A	2B		
CALGB (modified)	Painful mucositis not necessitating a change in oral intake	Painful mucositis restricting intake to soft foods	Painful mucositis restricting oral intake to liquids	Mucositis preventing oral intake	NA
CTC	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, edema, or ulcers but can swallow		Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutrition support	Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
CTCAE	Minimal symptoms, erythema of the mucosa	Symptomatic but can eat, patched ulceration or pseudomembranes		Symptomatic and cannot eat, confluent ulceration or pseudomembranes, bleeding with minor trauma	Symptomatic associated with life-threatening consequences, tissue necrosis, significant spontaneous bleeding
NCCTG	Soreness, erythema	Erythema, ulcers; patient can eat solid diet		Ulcers; patient requires liquid diet only	Alimentation not possible
RTOG	Mild dysphagia or odynophagia, may require topical anesthetic, nonnarcotic analgesic, or soft diet	Moderate dysphagia or odynophagia; may require narcotic analgesic or puree or liquid diet		Severe dysphagia or odynophagia with dehydration or weight loss (>15% from baseline) requiring nasogastric feeding, IV fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, or fistula
WHO	Soreness ± erythema; no ulceration	Erythema, ulcers; patient can swallow solid diet		Ulcers, extensive erythema; patient cannot swallow solid diet	Mucositis to the extent that alimentation is not possible

CALGB, Cancer and Leukemia Group B; CTC, Common Toxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenous; NA, not applicable; NCCTG, North Central Cancer Treatment Group; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organization.

### Assessment Tools Used to Evaluate the Severity of Mucositis

The severity of mucositis was evaluated using multiple assessment tools summarized in Table 2. The World Health Organization (WHO) scale<sup>5,24,26,27</sup> and the Radiation Therapy Oncology Group (RTOG) acute radiation-induced esophagitis morbidity scoring criteria<sup>7,19–21</sup> were the most frequently used scales to evaluate mucositis severity. Two studies used the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), a tool that uses a mixture of subjective, objective, and functional criteria.<sup>23,25,29</sup> The most commonly used terms in the aforementioned assessment tools were *erythema, ulcers/ulceration, soft/solid/liquid diet, and eat/swallow* (Table 2). Other subjective or patient-reported measures included symptoms such as mouth comfort and ease of eating,<sup>27</sup> maximum grade of mucositis,<sup>31</sup> and pain score according to a numerical rating scale.<sup>25</sup> Other objective measures reported in studies include changes in weight,<sup>7,19,25,26</sup> opioid use,<sup>22,25</sup> hospital length of stay,<sup>28</sup> duration of supplemental nutrition,<sup>25,28</sup> and the number of patients delaying treatment due to mucositis.<sup>7,19</sup>

### Efficacy of Oral Glutamine

The individual grades of mucositis reported in 11 of 15 studies are summarized in Table 3. Grade 4 mucositis was reported in 6 studies, among which 4 studies reported a lower incidence in the glutamine group compared with the control group.<sup>24–26,29</sup> Three of these 4 studies reported a statistically significant improvement with glutamine.<sup>24,26,29</sup> Although statistical significance was not reported in the study by Tsujimoto et al,<sup>25</sup> grade 4 mucositis was observed in 0% of the glutamine group compared with 25% in the control group. The 2 remaining studies showed a similar incidence of grade 4 mucositis with oral glutamine compared with control.<sup>27,31</sup> Among the 10 studies reporting grade 3 mucositis in patients, 7 studies observed a statistically significant reduction in the oral glutamine arm compared with the control group.<sup>5,7,19,20,24,26,29</sup> The 3 remaining studies reported comparable rates of grade 3 mucositis in patients in glutamine and control groups, although statistical significance was not evaluated.<sup>25,30,31</sup> All 11 studies reported grade 2 mucositis in the enrolled patients; 3 of these reported a significantly lower incidence in the glutamine group compared with the control group.<sup>5,20,29</sup> Additional 2 studies reported

**Table 3.** Efficacy of Oral Glutamine vs Control in Reducing the Severity of Mucositis.

Reference	Year	Grade 1 (% of Patients)		Grade 2 (% of Patients)		Grade 3 (% of Patients)		Grade 4 (% of Patients)	
		Glutamine	Control	Glutamine	Control	Glutamine	Control	Glutamine	Control
Choi et al <sup>29</sup>	2007	4/22 (18) <sup>NR</sup>	10/29 (35)	1/22 (5) <sup>a</sup>	5/29 (17)	1/22 (5) <sup>a</sup>	5/29 (17)	0/22 (0) <sup>a</sup>	1/29 (3)
Peterson et al <sup>5</sup>	2007	48/163 (29) <sup>NR</sup>	32/163 (20)	61/163 (37) <sup>a</sup>	70/163 (43)	2/163 (1) <sup>a</sup>	11/163 (7)	0/163 (0) <sup>NR</sup>	0/163 (0)
Vidal-Casariago et al <sup>26</sup>	2013	25/90 (28) <sup>a</sup>	3/27 (11)	20/90 (22)	6/27 (22)	14/90 (16) <sup>a</sup>	13/27 (48)	6/90 (6) <sup>a</sup>	3/27 (11)
Chattopadhyay et al <sup>24</sup>	2014	8/35 (23) <sup>NR</sup>	3/35 (9)	18/35 (51) <sup>NR</sup>	12/35 (34)	5/35 (14) <sup>a</sup>	13/35 (37)	1/35 (3) <sup>a</sup>	6/35 (17)
Topkan et al <sup>19</sup>	2009	—	—	6/22 (27) <sup>NR</sup>	7/22 (32)	0/22 (0) <sup>a</sup>	7/19 (37)	0/22 (0) <sup>NR</sup>	0/19 (0)
Topkan et al <sup>7</sup>	2012	—	—	20/56 (37) <sup>NR</sup>	16/48 (34)	3/56 (7) <sup>a</sup>	8/48 (17)	0/56 (0) <sup>NR</sup>	0/48 (0)
Tutanc et al <sup>20</sup>	2013	13/21 (62) <sup>a</sup>	2/25 (8)	7/21 (33) <sup>a</sup>	12/25 (48)	1/21 (5) <sup>a</sup>	11/25 (44)	0/21 (0) <sup>NR</sup>	0/25 (0)
Okuno et al <sup>31</sup>	1999	27/66 (41) <sup>NR</sup>	24/68 (35)	15/66 (23) <sup>NR</sup>	15/68 (22)	2/66 (3) <sup>NR</sup>	5/68 (7)	2/66 (3) <sup>NR</sup>	0/68 (0)
Jebb et al <sup>27</sup>	1994	2/17 (12) <sup>NR</sup>	1/17 (6)	2/17 (12) <sup>NR</sup>	6/17 (35)	0/17 (0) <sup>NR</sup>	0/17 (0)	5/17 (29) <sup>NR</sup>	4/17 (24)
Skubitz et al <sup>30</sup>	1996	7/14 (50) <sup>NR</sup>	4/17 (24)	0/14 (0) <sup>NR</sup>	9/14 (64)	0/14 (0) <sup>NR</sup>	1/14 (7)	—	—
Tsujimoto et al <sup>25</sup>	2015	0/20 (0) <sup>NR</sup>	0/20 (0)	2/20 (10) <sup>NR</sup>	0/0 (0)	18/20 (90) <sup>NR</sup>	15/20 (75)	0/20 (0) <sup>NR</sup>	5/20 (25)

—, data not available; <sup>NR</sup>, statistical significance not reported.

<sup>a</sup>Significant difference from control.

**Table 4.** Efficacy of Oral Glutamine vs Control in Duration, Time of Onset, and Maximum Grade of Mucositis.

Reference	Year	Average Weight Change, %		Average Duration of Mucositis, d		Average Time to Mucositis Onset, d		Average Maximum Grade of Mucositis	
		Glutamine	Control	Glutamine	Control	Glutamine	Control	Glutamine	Control
Vidal-Casariago et al <sup>26</sup>	2013	-6.6 <sup>a</sup>	-13.4	—	—	—	—	—	—
Chattopadhyay et al <sup>24</sup>	2014	—	—	6.6 <sup>a,b</sup>	9.2	16.5 <sup>a</sup>	7.1	—	—
Topkan et al <sup>19</sup>	2009	1.4 <sup>a,c</sup>	-3.8	—	—	22 <sup>a,c</sup>	16	—	—
Topkan et al <sup>7</sup>	2012	3.9 <sup>a,c</sup>	-4.9	—	—	24.5 <sup>a,d</sup>	16.4	—	—
Okuno et al <sup>31</sup>	1999	—	—	9 <sup>e</sup>	9	—	—	1.08 <sup>NR</sup>	1.02
Cockerham et al <sup>22</sup>	2000	—	—	10 <sup>a</sup>	14.1	—	—	2.5 <sup>a</sup>	3.22
Coughlin Dickson et al <sup>28</sup>	2000	—	—	13 <sup>c</sup>	13	—	—	3 <sup>NR,c</sup>	2
Skubitz et al <sup>30</sup>	1996	—	—	2.7 <sup>a</sup>	9.9	—	—	0-1 <sup>a,c</sup>	2A
Gul et al <sup>21</sup>	2015	—	—	6.5 <sup>a,f</sup>	17.5 <sup>f</sup>	21.8 <sup>f</sup>	16 <sup>f</sup>	0.68 <sup>a</sup>	1.87
Tsujimoto et al <sup>25</sup>	2015	-3.6	-6.0	33.6 <sup>f</sup>	35 <sup>f</sup>	16.1 <sup>f</sup>	14.7 <sup>f</sup>	2.9 <sup>a</sup>	3.3

—, data not available; <sup>NR</sup>, statistical significance not reported.

<sup>a</sup>Significant difference from control.

<sup>b</sup>Grade 3 or 4 mucositis.

<sup>c</sup>Median rather than mean.

<sup>d</sup>Maximum grade mucositis.

<sup>e</sup>Patient-reported mucositis.

<sup>f</sup>Conversion of data from weeks in the original report to days.

lower grade 2 mucositis with glutamine without evaluating statistical significance.<sup>27,30</sup> The incidence of grade 2 mucositis was similar between the groups in 4 studies<sup>7,19,26,31</sup> and slightly higher in 2 studies.<sup>24,25</sup> The proportion of patients with grade 1 mucositis was often higher in the glutamine groups compared with the control groups (Table 3). However, this is likely due to a lower number of patients progressing to more severe grades (3 and 4) of mucositis. Last, 1 study by Li et al<sup>23</sup> reported severity of combined grades 1–2 and 3–4 stomatitis rather than individual grades; no significant difference between glutamine and placebo arms was reported.

The subjective and objective measures for evaluating the efficacy of oral glutamine vs control in 10 of 15 studies are

summarized in Table 4. These measures included average weight change as well as average (mean or median as reported per individual studies) duration, time of onset, and/or maximum grade of mucositis. All 4 studies reporting average weight change had a favorable outcome with oral glutamine treatment. Two studies observed weight gain in the glutamine group compared with weight loss in the control group.<sup>7,19</sup> The remaining 2 studies reported less weight lost in the glutamine compared with the control group<sup>25,26</sup>; only 1 of these studies reported a statistically significant difference.<sup>26</sup>

Seven studies reported average duration of mucositis. Among these, 4 reported a statistically significant reduction with glutamine,<sup>21,22,24,30</sup> and 3 reported no significant difference.<sup>25,28,31</sup> Of

the 5 studies reporting time to mucositis onset, 3 showed a statistically significant longer average time of mucositis onset in the glutamine group.<sup>7,19,21,24,25</sup> Among the 6 studies recording average maximum mucositis grade, 4 studies showed a significant decrease in the glutamine group,<sup>21,22,25,30</sup> 1 study showed no difference,<sup>31</sup> and 1 study showed an increase in the median maximum grade mucositis grade with oral glutamine.<sup>28</sup>

Various other outcome measures of glutamine efficacy were also reported. A study by Gul et al<sup>21</sup> reported a trend toward a significant decrease in overall incidence of mucositis in the oral glutamine arm compared with control (58% vs 100%,  $P = .051$ ). Oral glutamine also improved the ulceration scores (0.23 vs 0.32,  $P = .013$ )<sup>5</sup> and was associated with a 23.5% reduction in nasogastric tube feedings ( $P = .04$ ).<sup>26</sup> Similarly, Tsujimoto et al<sup>25</sup> reported the mean duration of supplemental nutrition (enteral or parenteral) required due to severe mucositis to be significantly shorter in the glutamine group vs control (18 vs 27 days,  $P = .046$ ). However, oral glutamine did not improve the median days on parental nutrition (PN) compared with placebo in another study (22 vs 22 days,  $P = .84$ ).<sup>28</sup> Skubitz et al<sup>30</sup> reported that oral glutamine reduced the need for chemotherapy dose reductions due to mucositis in 8 of 14 patients. The number of patients delaying treatment due to mucositis was lower with oral glutamine vs control in 2 studies (7.1% vs 20.8%,  $P = .04$ <sup>7</sup> and 13.6% vs 36.8%,  $P = .08$ <sup>19</sup>), with 1 study reaching statistical significance.<sup>7</sup> While Tsujimoto et al<sup>25</sup> showed significantly lower patient-reported pain scores with oral glutamine treatment ( $P < .05$ ), no difference in oral pain was evident in the study by Peterson et al.<sup>5</sup> Studies also reported significantly fewer days of parenteral patient-controlled analgesia (PCA) morphine (5.22 vs 0.0 days,  $P = .002$ ),<sup>22</sup> a trend toward shorter duration of opioid use (10.89 vs 6.75 days,  $P = .051$ <sup>22</sup>; 19 vs 28 days,  $P = .029$ <sup>25</sup>), and a clinically relevant lower total dose of opioids (2370 mg vs 3959 mg in morphine equivalents,  $P = .101$ )<sup>25</sup> with oral glutamine use. However, the study by Vidal-Casariago et al<sup>26</sup> reported no differences in opioid use in the glutamine group vs control.

Not all patient-reported findings demonstrated a benefit with oral glutamine. In the study by Okuno et al,<sup>31</sup> the patient-reported mean maximum grades of mucositis showed no significant difference in the glutamine group vs control (1.19 vs 0.98, respectively,  $P = .58$ ). In addition, patient-reported mouth comfort and ease of eating showed no significant difference with oral glutamine in the study by Jebb et al.<sup>27</sup>

### Adverse Effects of Oral Glutamine

Of 15 studies reviewed, 7 reported adverse reactions.<sup>5,7,19,20,25,27,31</sup> In 1 retrospective study, rates of nausea were similar between glutamine and control groups (grade 1, 32.1% vs 29.2%; grade 2, 19.6% vs 16.7%) during the 7 days prior to receiving radiation therapy.<sup>7</sup> Another prospective study reported a similar incidence of subjective adverse events between glutamine and control arms (nausea, 8.8% vs 8.3%; vomiting, 1.6% vs 1.9%;

dry mouth, 5.2% vs 4.1%; anorexia, 0.7% vs 0.3%).<sup>5</sup> Five other studies reported that no adverse events were observed, although methods for adverse event determinations were not clearly defined.<sup>19,20,25,27,31</sup>

It is important to note that the complications seen with IV glutamine in the Pytlik et al<sup>16</sup> study, such as increased oral mucositis and increased disease recurrence after stem cell transplantation with a nonsignificant increase in mortality, were not reported with oral glutamine in any of the identified studies included in this review. Of the 15 studies reviewed, 3 reported no significant difference in cancer-related clinical outcomes with oral glutamine compared with control,<sup>7,23,25</sup> while the remaining studies did not report clinical outcomes. Specifically, the median overall survival, locoregional progression-free survival, and progression-free survival for oral glutamine vs control groups were similar (21.4 vs 20.4 months,  $P = .23$ ; 11.3 vs 14.2 months,  $P = .11$ ; and 10.2 vs 9.0 months,  $P = .19$ , respectively) in 1 study.<sup>7</sup> In addition, no significant differences were seen in the number of patients with tumor response measured by complete response (65% vs 60%), partial response (25% vs 25%), stable disease (10% vs 0%), and progressive disease (0% vs 10%) in the oral glutamine vs control groups in another study.<sup>25</sup> Last, another study found the decrease in tumor size was not significantly different between glutamine and placebo groups ( $P < .05$ ).<sup>23</sup>

### Glutamine Dosing Regimen

The most frequently used dose of oral glutamine was 30 g/d,<sup>7,19–21,23,25,26,28,29</sup> usually given in 3 divided doses, as this was shown to be effective in animal studies and safe in human studies.<sup>32,33</sup> Most studies used a powdered form of glutamine mixed with a beverage or soft/moist food,<sup>28,29</sup> water or fruit juice,<sup>7,19–21,23,24,27</sup> or water with flavored syrup.<sup>22,30</sup> Six studies used a swish-and-swallow method of oral administration.<sup>5,22,24,27,30,31</sup> Peterson et al<sup>5</sup> used a relatively smaller dose of glutamine (7.5 g/d in 3 divided doses) swished and swallowed using a novel, proprietary drug delivery system that has shown to facilitate higher uptake of glutamine by epithelial oral mucosal cells compared with other available dosage forms. Other dosage regimens include 8 g/d in 2 divided doses,<sup>30,31</sup> 10 g/d as a single dose,<sup>24</sup> 24 g/d in 6 divided doses,<sup>22</sup> and 16 g/d in 4 divided doses.<sup>27</sup>

In addition to the differing doses, the time of initiation and duration of glutamine varied between studies (Table 1). Eight studies initiated glutamine on day 1 of anticancer treatment,<sup>5,20,22–25,28,30,31</sup> while the remaining studies initiated glutamine before chemotherapy and/or radiation.<sup>7,19,21,26,27,29</sup> All studies gave glutamine for the duration of anticancer treatment, and the majority continued glutamine after the anticancer treatment had ceased.<sup>5,7,19–22,27–31</sup> In 1 study, oral glutamine therapy was shown to be beneficial only when initiated prior to anticancer therapy or on day 1 of cancer therapy and not when delayed after starting the chemotherapy and/or radiation.<sup>26</sup>

## Discussion

In this systematic review, studies evaluating oral glutamine to prevent mucositis in adult patients with cancer treated with chemotherapy and/or radiation were reviewed. In most studies reporting different grades of mucositis, glutamine was shown to significantly reduce the severity of mucositis.<sup>5,7,19,20,24,26,29</sup> In addition, oral glutamine was shown to significantly reduce weight loss<sup>7,19,26</sup> as well as the average duration,<sup>21,22,24,30</sup> time of onset,<sup>7,19,24</sup> and/or maximum grade of mucositis<sup>21,22,25,30</sup> in most studies reporting these measures. Oral glutamine was found to be safe at doses up to 30 g/d with no difference reported in adverse events vs control groups<sup>5,7,19,20,25,27,31</sup>; however, not all identified studies evaluated drug toxicity. Overall, oral glutamine was shown to be effective in 11 of the 15 studies included in the systematic review.

The findings of this systematic review should be interpreted in light of several limitations. The high heterogeneity of the patient populations in the studies examined makes it difficult to determine which patient populations would benefit the most from oral glutamine, especially considering that certain cancer types and treatment regimens are associated with a higher risk of severe mucositis. For example, the treatment combination of platinum-based chemotherapy plus radiation therapy (XRT) is associated with a 64% incidence of grade 3 and 4 oral mucositis.<sup>10</sup> Furthermore, the addition of XRT to 5-fluorouracil (5-FU)-based and irinotecan-based regimens can increase the risk of grade 3 and 4 oral mucositis to >30%.<sup>10</sup> These regimens are especially common in head/neck and esophageal cancers and thus are associated with an increased risk of grade 3 and 4 oral mucositis between 40% and 50%.<sup>10</sup> Furthermore, the retrospective nature of many studies may have resulted in an increased number of unmeasured confounding variables and bias.<sup>7,19,20,22,26</sup> However, all the retrospective studies evaluated oral glutamine in comparison to a control arm, and all prospective studies showed similar efficacy results. In addition, most studies had a relatively small sample size, which may have resulted in underpowered studies unable to find significant differences in outcomes. Inconsistencies in the assessment tools to evaluate mucositis were also noted. While the categories in these tools were similar, subjective variations in interpretation of the grading criteria cannot be ruled out. Universal use of a single severity assessment tool would significantly enhance comparison between studies. Another limitation is the dosing and dosage form inconsistencies with oral glutamine. The most common dosing regimen was 30 g/d in 3 divided doses, with other regimens ranging from 7.5–24 g/d. Also, glutamine was mixed with liquids or soft food in all studies except for the study by Peterson et al,<sup>5</sup> which evaluated a special formulation of oral glutamine that facilitates a rapid uptake of glutamine by mucosa. Despite the variability in oral glutamine doses and formulations, most studies still demonstrated improved mucositis in patients given oral glutamine in comparison to control. Future studies should investigate different dosing regimens of

oral glutamine to determine the lowest dose sufficient to prevent mucositis in patients with cancer. Furthermore, various glutamine formulations should be investigated as it is hypothesized that “thicker” formulations might increase the contact time with mucosa, resulting in enhanced glutamine delivery and improved efficacy. This concept is demonstrated in the study by Peterson et al,<sup>5</sup> which used a novel drug delivery system for oral glutamine and reported effective prevention of mucositis despite using a small dose of glutamine.

Four of the 15 studies included in the systematic review showed no difference in mucositis severity with the administration of oral glutamine.<sup>23,27,28,31</sup> Several reasons can be hypothesized for these findings. Okuno et al<sup>31</sup> stated that oral cryotherapy before chemotherapy might have blunted the beneficial effects of oral glutamine. In addition, a lower daily dose of oral glutamine (8 g/d) was used, which may have contributed to the lack of glutamine efficacy. However, another study using 5-FU chemotherapy with oral cryotherapy demonstrated efficacy with a higher dose of oral glutamine (30 g/d).<sup>29</sup> Jebb et al<sup>27</sup> noted that a relatively lower dose of 16 g/d in 4 divided doses might be a contributing factor for the lack of efficacy observed in their study. However, other studies have demonstrated effectiveness of oral glutamine at even lower daily doses.<sup>24,30</sup> Another factor that may affect the efficacy of glutamine is adherence to therapy. Coghlin Dickson et al<sup>28</sup> had varied and often much lower daily consumption than the treatment protocol. Interestingly, when only patients consuming greater than the lowest suggested daily dose were evaluated ( $\geq 0.285$  g/kg/d, N = 27), the glutamine group had a shorter median length of stay by 6 days and 5 fewer median days on PN, although these findings were not statistically significant. We recommend future studies consider evaluating the efficacy of oral glutamine in relation to its daily weight-based consumption. Assessing the glutamine treatment durations and its impact on the differences in the reported glutamine efficacy can be difficult as the patient population, cancer type, and treatment regimen varied substantially in different studies. However, it can also be an important factor influencing the efficacy of oral glutamine.

The exact mechanism by which oral glutamine prevents mucositis is not clear. Glutamine is the primary oxidative fuel of the digestive tract epithelium and helps maintain integrity of the gut structure during normal and stressful conditions.<sup>34–36</sup> These properties led to the hypothesis that glutamine is beneficial to prevent mucositis in patients at high risk. Significant amounts of glutamine are provided by skeletal muscles during hypercatabolic states such as cancer, causing marked glutamine depletion over time.<sup>37–39</sup> In this depleted state, synthesis alone is not sufficient to replenish glutamine, making it a conditionally essential amino acid. There have been concerns that glutamine may promote tumor growth.<sup>40,41</sup> However, some in vivo studies have shown that glutamine may in fact enhance sensitivity of the tumor cells to chemotherapy.<sup>42–44</sup> The local effects of oral glutamine in GI mucosa may actually be different from its systemic effect, as indicated by the differences in

the efficacy and safety of oral vs IV glutamine.<sup>16,19</sup> Additional studies may be necessary to investigate the differential action of glutamine in healthy vs cancer cells. Furthermore, long-term safety of glutamine should be evaluated in future clinical studies. As a result of the favorable safety profile and efficacy exhibited in smaller trials included in this systematic review, large multicenter randomized placebo-controlled studies are warranted to further evaluate the efficacy of oral glutamine, especially in cancer types and treatment regimens with a higher incidence of severe mucositis.

## Conclusion

In conclusion, most of the studies we reviewed demonstrated favorable efficacy of oral glutamine, initiated 0–7 days before chemotherapy and/or radiation at a maximum dose of 30 g/d, in decreasing the duration and severity of mucositis in adult patients with cancer undergoing chemotherapy and/or radiation. However, most of the studies were conducted in a small number of patients, and several studies were retrospective. Despite these limitations, the favorable efficacy of oral glutamine, coupled with its low toxicity profile, provides a strong rationale for large multicenter randomized placebo-controlled studies to further evaluate its efficacy and safety to prevent mucositis in patients with cancer receiving chemotherapy and/or radiation. Future studies should evaluate optimizing the dose and duration of oral glutamine, which may vary based on cancer type and treatment modalities/regimens.

## Statement of Authorship

C. Sayles and M. V. Trivedi contributed to conception/design of the research; C. Sayles, S. C. Hickerson, R. R. Bhat, J. Hall, K. W. Garey, and M. V. Trivedi contributed to acquisition, analysis, or interpretation of the data; C. Sayles and S. C. Hickerson drafted the manuscript; C. Sayles, S. C. Hickerson, R. R. Bhat, J. Hall, K. W. Garey, and M. V. Trivedi critically revised the manuscript; and C. Sayles, S. C. Hickerson, R. R. Bhat, J. Hall, K. W. Garey, and M. V. Trivedi agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

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