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Alleviation of Cancer Therapy-Induced Gastrointestinal Toxicity using an Amino Acid Medical Food

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Abstract

Gastrointestinal toxicity is common during cancer therapy, and treatment options are often unsatisfactory. Preclinical studies using a proprietary mixture of amino acids demonstrated reductions in mucositis and gastrointestinal toxicity following irradiation. This retrospective feasibility analysis was conducted to provide initial information regarding the potential for an amino acid medical food to alleviate gastrointestinal toxicity in cancer patients undergoing chemotherapy and/or radiation therapy. Patients were eligible to receive a 16-day supply of an amino acid medical food (enterade®) if they developed gastrointestinal toxicity during chemotherapy and/or radiotherapy. Patients completed a questionnaire before starting the product and again 14 days later. Tumor and treatment characteristics were reported, as were type and severity of gastrointestinal symptoms, other adverse effects (weight loss, dehydration, malaise) and current weight. Changes in symptom severity and in a composite score (the number of symptoms with improvement divided by the total number of symptoms) were determined for diarrhea, nausea, dehydration, weight loss, and malaise. Of the 154 enrolled patients, 118 completed both questionnaires. Of these, 15 patients did not use the amino acid medical food, 43 used it for 1-6 days, and 60 used it for ≥7 days. Among the individual symptoms, statistically significant improvements were noted for diarrhea, dehydration and weight maintenance. A 78% improvement in the composite symptom score was reported in patients who used the product for >7 days, compared to 46% improvement in those who used it for 1-6 days and 7% improvement in those who did not use it at all. In conclusion, use of an amino acid medical food may be associated with reduced gastrointestinal toxicity in patients undergoing cancer therapy. Additional prospective clinical studies to evaluate beneficial effects of this medical food are warranted.

Keywords: Amino acids; Dehydration; Diarrhea; Fluid balance; Medical-food

Introduction

Gastrointestinal symptoms are a near-universal problem among patients treated for cancer. Gastrointestinal toxicity can manifest as diarrhea, nausea, vomiting, bloating, pain, weight loss and/or dehydration. Acute or chronic dehydration and diarrhea are frequently experienced by patients receiving radiotherapy and chemotherapy [1-6], and the incidence of nausea and vomiting has been reported to be as high as 70% [7]. In addition to reducing quality of life, gastrointestinal toxicity and other symptoms in cancer patients can lead to premature discontinuation of therapy and/or dose reductions of chemotherapy and radiation, impacting efficacy of treatment [6]. Additionally, most patients, particularly those with the worst symptoms, suffer multiple gastrointestinal symptoms simultaneously. Nausea, diarrhea, vomiting, and loss of appetite cumulatively lead to malnutrition and dehydration, which can be life threatening and result in hospitalization and premature death [4,6].

Despite the high prevalence of enteritis associated with cancer therapy, the evidence base for treatment is limited. Current treatment of acute enteritis includes anti-diarrheal medications to reduce stool frequency and volume, intravenous fluids for dehydration, anti-emetics for nausea, smectite as an adsorbent of bile salts, opioids to relieve pain, and steroids to relieve inflammation. None of these treatments are fully satisfactory, and the treatments have side effects that themselves can worsen or cause gastrointestinal symptoms [1,8-11].

The consumption of oral rehydration solutions containing glucose is frequently promoted to treat diarrhea, but sugars may be absorbed poorly when the intestine is damaged [12]. In contrast, certain amino acids have been shown to support functions of the intestinal mucosa when damaged. The commercial beverage enterade® is a glucose-free, amino acid-based medical food containing specific amino acids, namely aspartic acid, valine, serine, threonine and tyrosine, in addition to electrolytes and a non-sugar sweetener. enterade® is glucose-free and has been used safely by more than 30,000 patients suffering from toxic gut symptoms in association with cancer therapies. The amino acids have shown to promote tightening of the mucosal barrier, proliferation of crypt cells, increases in villous height and absorption of fluid, electrolytes and nutrients following radiation in pre-clinical models [13,14]. In addition, this amino acid mixture reduced weight loss and promoted survival in irradiated mice [13]. A case study [15] of drastically improved cancer immune therapy-induced diarrhea following treatment with enterade® led to our hypothesis that enterade® could provide a safe alleviation for symptoms of gastrointestinal toxicity and dehydration in oncology patients. This feasibility study was performed in preparation for a randomized clinical trial and to provide a signal of improvement.

Materials and Methods

Study Design

The objective of this feasibility study, featuring a retrospective analysis of prospectively collected data, was to determine if consumption of enterade® was associated with a decrease in patient-reported outcomes of gastrointestinal toxicity during radiotherapy and/or chemotherapy. This 154-patient study was designed to evaluate reported outcomes in cancer patients provided with enterade® to assist with management of gastrointestinal symptoms secondary to radiation therapy or chemotherapy. The gastrointestinal symptoms prospectively assessed from January 2016 to October 2016 included diarrhea, nausea, dehydration, weight loss, malaise, cramping, mucositis, bloating, esophagitis, dry mouth and oral pain.

Patients

Cancer patients >21 years' old who had care managed at 21st Century Oncology, were treated with radiation therapy or chemotherapy and had symptoms of gastrointestinal toxicity (diarrhea, nausea, oral mucositis, bloating and/or cramping) or other adverse effects of cancer therapy (weight loss, dehydration, malaise) were offered a 16-day trial of enterade® by their treating physician. Patients with all cancer types were eligible to receive the product, as were those who had undergone recent surgery or recent/concurrent chemotherapy. Patients with an ECOG performance status 3 or greater, metastasis or active infection were excluded from the study, as were pregnant and breast-feeding women. Patients were recruited on a consecutive manner and were not allowed to be enrolled more than one time. The protocol to retrospectively review the medical chart of these patients was approved by a committee of experts from the New England IRB.

Treatments and data collection

Physicians and staff were trained by the medical education team of Entrinsic Health Solutions, Inc., on the appropriate indications and instructions for use of enterade® and is was used as a standard procedure. At the physician's discretion, a patient who was experiencing gastrointestinal toxicity due to chemotherapy or radiation therapy was offered an initial two-day supply (two 8-oz bottles each of orange- and vanilla-flavored enterade®). The patients were directed to order an additional 14-day supply of the preferred flavor from the enterade® website; this supply was sent overnight, free of charge. The patients were advised to consume two bottles daily for at least seven days. Patients continued standard-of-care therapy for diarrhea and nausea (loperamide and ondansetron) that was preferred by the site while receiving the enterade®. The study had no influence on the prescribing of other medications used at the institution.

Physicians and nurses were asked to have the patients report gastrointestinal toxicity by completing a written symptom inventory with the assistance of the healthcare provider prior to receiving the two-day trial of enterade®. This non-validated inventory created by the clinical site directed patients to provide information about their type of cancer, current treatment, type and severity of gastrointestinal symptoms (nausea, diarrhea, oral mucositis, bloating, cramping) and other adverse effects of cancer therapy (weight loss, dehydration, malaise), current medications and current weight. Patients were advised to classify diarrhea as mild (three days of < 3 loose stools per day), moderate (more than three days of 3-4 stools per day) or severe (more than three days of >4 stools per day). Fourteen days after receiving the two-day trial of enterade®, each patient was asked to complete a similar inventory describing product use, type and severity (none/resolved, mild, moderate, severe) of toxicity symptoms, degree of improvement for toxicity symptoms (none, mild, moderate, significant), current weight and comments about the enterade®. These post-intervention inventories were completed by the patient and were a formal part of the patient care. Information from both inventories was entered by the medical staff into each patient's medical record. Retrospective chart review from 21st Century Oncology medical records was performed by the clinic staff from November 2016 to February 2017. Endpoint collection and analysis was done using anonymous medical chart data.

Endpoints

Changes in gastrointestinal symptoms after 14 days were compared for patients who did not use enterade®, who used the product for 1-6 days, and who used enterade® for at least 7 days. A 10-month retrospective review of patient charts was performed. Duration of enterade® use was based on patient reports in the

14-day symptom inventories. Patients were considered to have consumed no enterade® if they used the product for less than one day (less than two 8-oz bottles). Diarrhea, nausea, dehydration oral mucositis, malaise, cramping and bloating were assessed based on patients' subjective reports of improvement, and weight loss was assessed by comparing the initial and final weights reported by the patients. Changes in gastrointestinal symptoms after 14 days were compared for patients who did not use enterade®, who used the product for 1-6 days, and who used enterade® for at least 7 days. Improvement outcomes were evaluated for individual symptoms based on patient-reported levels of improvement and using a composite score for collective improvement in the five most common symptoms (diarrhea, nausea, dehydration, malaise and weight loss). The composite score was calculated for each enterade® usage group by dividing the total number of reported symptoms with improvement (symptoms from the list of five for which patients noted "mild," "moderate" or "significant" improvement on the day 14 symptom inventory) by the total number of reports for the five symptoms on the initial symptom inventories.

Statistical Analysis

Statistical analysis was conducted using JMP software (version 13.0, SAS Institute, Cary, NC). No power calculations were done for this study. A likelihood ratio χ^2 test was utilized to assess the impact of duration of enterade® use on symptom improvement (both for individual improvement and for the composite score). A Cochran Mantel Haenszel row means score χ^2 test was utilized to assess the effect of the number of initial symptoms on the degree of symptom improvement during the intervention period. Significance was accepted at $P < 0.05$.

Results

Of the 154 cancer patients with gastrointestinal toxicity who received enterade®, 21 failed to note the duration of enterade® use and 15 failed to complete the day 14 survey (Figure 1).

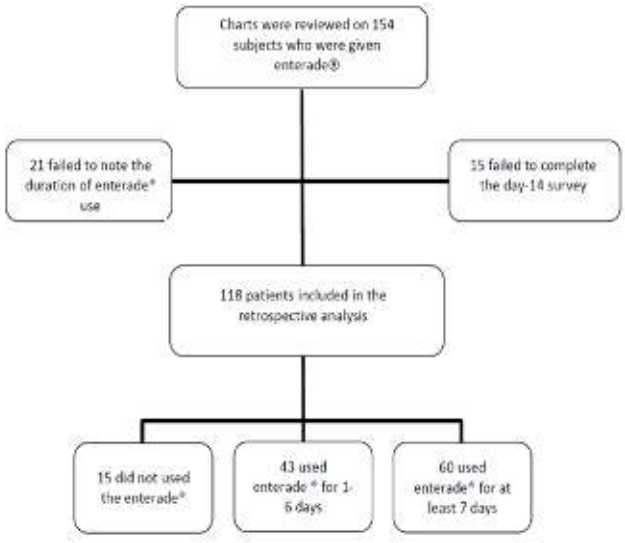

Figure 1: Study design and flow chart.

Of the 118 patients included in the retrospective analysis, 60 used enterade® for the recommended duration of seven or more days, 43 used it for 1-6 days and 15 did not use the enterade® during the 14-day period. Age and sex distributions were similar for the recommended-, low- and no-enterade® usage groups (Table 1), as were the tumor types (Table 2) and the initial severities of symptoms (Tables 2,3). Colon/rectal cancer was the most common primary cancer (19% of patients), followed by lung and head/neck malignancies (17% and 14% of patients, respectively; Table 2). More than half of the patients reported more than one gastrointestinal symptom on presentation, and the distributions of diarrhea, dehydration and malaise were similar for the three enterade® usage groups (Tables 2,3). Diarrhea was the most common complaint, experienced by 50% of patients, followed by nausea and dehydration (both reported by 36% of patients), malaise (32% of patients) and weight loss (31% of patients) (Table 3).

		enterade® consumption group		
	Total	**0 days**	**1-6 days**	**≥ 7 days**
Total number of patients	118	15	43	60
Males	56	7	24	25
Females	62	8	19	35
Average age in years*	71	68	70	72
(min, max)	(24, >89)	(24, >89)	(42 , >89)	(41, >89)
* There was no significant difference in average age between the three groups.				

Table 1: Patient demographics.

Cancer types and initial gastrointestinal symptoms (number, %) for patients who used enterade® >7 days (n=60)								
Cancer site of origin	Diarrhea	Dehydration	Weight loss	Nausea	Malaise	Bloating	Cramping	Mucositis
Colon/rectal, 14 (23.3%)	10 (71%)	8 (57%)	10 (71%)	10 (71%)	6 (42%)	4 (28%)	3 (21%)	2 (14%)
Lung, 12 (20%)	4 (33%)	4 (33%)	4 (33%)	9 (75%)	6 (50%)	0 (0%)	6 (55%)	0 (0%)
Head/neck, 9 (15%)	1 (11%)	5 (55%)	3 (33%)	5 (55%)	6 (66%)	1 (11%)	2 (22%)	0 (0%)
Prostate, 6 (9.5%)	3 (50%)	1 (16%)	1 (16%)	0 (0%)	2 (33%)	1 (16%)	1 (16%)	0 (0%)
Breast, 5 (8%)	2 (40%)	4 (80%)	3 (60%)	4 (80%)	5(100%)	1 (20%)	0 (0%)	0 (0%)
Other, 14 (23.3%)	7 (50%)	10 (71%)	5 (35%)	6 (42%)	3 (21%)	0 (0%)	2 (14%)	0 (0%)
Cancer types and initial gastrointestinal symptoms (number, %) for patients who used enterade® 1-6 days (n=43)								
Cancer site of origin	Diarrhea	Dehydration	Weight loss	Nausea	Malaise	Bloating	Cramping	Mucositis
Colon/rectal, 5 (11.6%)	4 (80%)	1 (20%)	2 (40%)	1 (20%)	1 (25%)	2 (40%)	1 (20%)	0 (%)
Lung, 6 (14%)	3 (50%)	2 (33%)	2 (33%)	2 (33%)	0 (0%)	0 (0%)	3 (50%)	0 (0%)
Head/neck, 11 (25.5%)	4 (36%)	4 (36%)	1 (9%)	2 (18%)	2 (18%)	2 (18%)	1 (9%)	0 (0%)
Prostate, 9 (21%)	5 (55%)	1 (11%)	1 (11%)	2 (22%)	2 (22%)	0 (0%)	0 (0%)	0 (0%)
Breast, 2 (4.6%)	1 (50%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Other, 10 (23.2%)	6 (60%)	2 (20%)	3 (30%)	2 (20%)	2 (20%)	1 (10%)	2 (20%)	2 (20%)
Cancer types and initial gastrointestinal symptoms (number, %) for patients who did not use enterade® (n=15)								
Cancer site of origin	Diarrhea	Dehydration	Weight loss	Nausea	Malaise	Bloating	Cramping	Mucositis
Colon/rectal, 3 (11.6%)	2 (66%)	0 (0%)	1 (33%)	0 (0%)	1 (33%)	0 (0%)	0 (0%)	0 (%)
Lung, 0 (14%)	0 (0%)	0 (0%)	0 (33%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Head/neck, 5 (25.5%)	2 (40%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prostate, 4 (21%)	3 (75%)	0 (0%)	1 (25%)	0 (0%)	1 (25%)	0 (0%)	0 (0%)	0 (0%)
Breast, 1 (4.6%)	1 (50%)	0 (0%)	0 (0%)	1 (100%)	0 0%)	0 (0%)	0 (0%)	0 (0%)
Other, 2 (23.2%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	2 (20%)

Table 2: Cancer types and initial gastrointestinal toxicity symptoms.

		enterade® consumption group		
	Total	**0 days**	**1-6 days**	**≥ 7 days**
Number	118	15	43	60
Males	56	7	24	25
Females	62	8	19	35
Age in years (min, max)	71 (24, >89)	68 (24, >89)	70 (42 , >89)	72 (41, >89)
Initially reported symptoms*				
Diarrhea	60 (50%)	10 (66%)	23 (53%)	27 (45%)
Nausea	43 (36%)	1 (7%)	10 (23%)	32 (53%)
Dehydration	43 (36%)	1 (7%)	10 (23%)	32 (53%)
Malaise	38 (32%)	3 (20%)	7 (31%)	28 (69%)
Weight loss	37 (31%)	2 (13%)	9 (20%)	26 (43%)
Cramping	18 (15%)	0 (0%)	3 (6%)	15 (25%)
Mucositis	16 (13%)	3 (20%)	5 (11%)	8 (13%)
Bloating	11 (9%)	1 (7%)	1 (2%)	9 (15%)
Severity of initially reported symptoms**				
Severe	34 (29%)	4 (20%)	13 (27%)	17 (31%)
Moderate	64 (54%)	15 (75%)	21 (43%)	28 (52%)
Mild	31 (26%)	7 (35%)	15 (31%)	9 (17%)

*The differences in symptom severity between the 1-6 day and >7-day enterade® groups were not statistically significant for diarrhea, vomiting, dehydration, weight loss or malaise.

**Initial symptom severity is shown as the number of patients in each group reporting at least one symptom at the given severity level. The severity level was defined as the severity of the patient's worst symptom.

Table 3: Type and severity of initial symptoms.

Of the 27 patients who reported diarrhea at the time of receiving enterade® and used the product for more than 7 days, 20 (74%) reported improvement (Figure 2A). One of the 10 patients (10%) who did not use enterade® reported an improvement in diarrhea. Of the 23 patients who used enterade® for 1-6 days, 11 (48%) noted an improvement (Figure 2A). There was a significant improvement in diarrhea for the patients who used enterade® for at least 7 days (n=27) compared to those who used enterade® for less than 7 days (n=33) ($p < 0.05$). The one patient whose diarrhea improved from "severe" to "resolved" had consumed enterade® for > 7 days. Of the five patients whose symptoms improved from "severe" to "mild," three had consumed enterade® for > 7 days, two for 1-6 days.

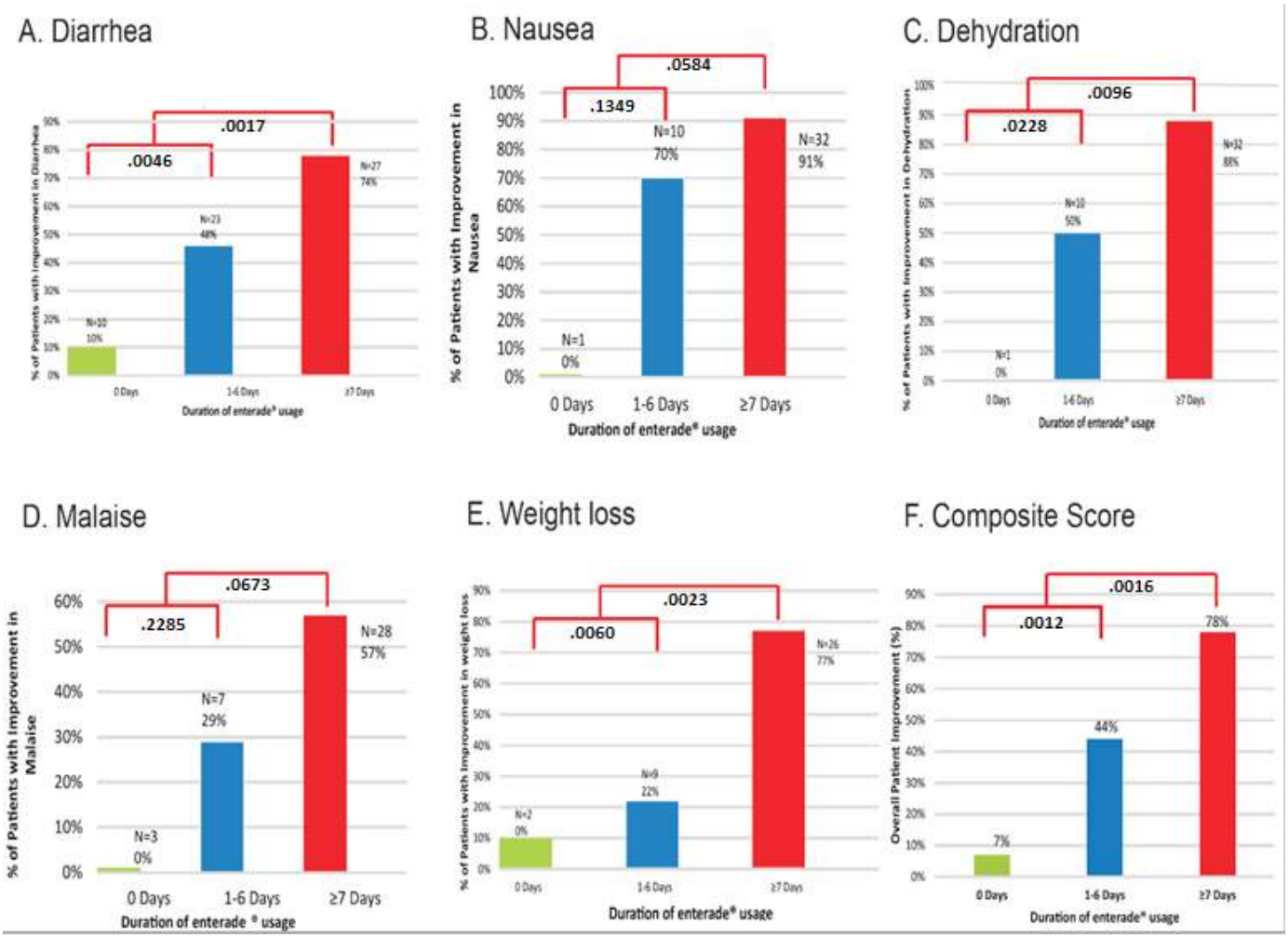

Figure 2: Effects of different durations of enterade® use on gastrointestinal symptoms in cancer patients. The percent of patients reporting improvement in diarrhea (A), nausea (B) dehydration (C) malaise (D) and weight maintenance (E) were obtained from symptom inventories in patient charts. The composite score (F) reflects collective improvement in all five of these symptoms. Precise p-values shown to four decimal places.

Of the 32 patients with initial nausea who used enterade® for ≥7 days, 29 (91%) reported improvement (Figure 2B). No improvement in nausea was reported for the single patient with this symptom who did not use enterade®. Of the ten patients who used enterade® from 1-6 days and had nausea as an initial complaint, 7 (70%) reported improvement (Figure 2B). There was a trend toward improvement for the patients who used enterade® for at least 7 days (n=32) compared to those who used it for less than 7 days (n=11) ($p > 0.05$). Both of the patients whose nausea improved from "severe" to "resolved" had consumed enterade® for > 7 days.

Of the 32 patients subjectively reporting dehydration who used enterade® for ≥7 days, 28 (88%) reported improvement (Figure 2C). No improvement in dehydration was reported for the single patient with this symptom who did not use enterade®. Of the ten patients who used enterade® from 1-6 days and noted dehydration as an initial complaint, five (50%) reported improvement (Figure 2C). There was a significant improvement in self-reported dehydration for the patients who used enterade® for at least 7 days (n=32) compared to those who used enterade® for less than one week (n=11) ($p < 0.05$). Of the six patients whose rating of dehydration improved from "severe" to "resolved," all had used enterade® for > 7 days; of the nine patients whose rating of dehydration improved from "severe" to "mild," eight had used enterade® for > 7 days and the remaining patient had used it for 1-6 days.

Of the 28 patients reporting malaise who used enterade® for ≥7 days, 16 (57%) reported improvement (Figure 2D). No improvement was reported for the three patients with malaise who did not use enterade®. Of the seven patients who used enterade® from 1-6 days and recorded malaise as an initial complaint, two (29%) reported improvement (Figure 2D). There was a trend toward improvement for the patients who used enterade® for ≥7 days (n=28) compared to those who used the product for less than seven days (n=10) ($p > 0.05$).

Of the 26 patients initially reporting weight loss who used enterade® for ≥7 days, 20 (77%) maintained or gained weight during the two weeks of the intervention (Figure 2E). In contrast, weight loss was reported for the two patients with this initial symptom who did not use enterade®. Of the nine patients who used enterade® from 1-6 days and noted weight loss as an initial complaint, two (22%) maintained weight during the two weeks (Figure 2E). There was significant improvement in weight maintenance for the patients who used enterade® for ≥7 days (n=26) compared to those who used it for less than seven days (n=11) ($p < 0.05$).

Since many patients reported multiple symptoms in the initial survey, a composite measure was calculated to evaluate improvement in the five most common symptoms as a whole based on the duration of enterade® usage. When diarrhea, nausea, dehydration, malaise and weight loss were taken together, a total of 276 symptoms were reported in the initial symptom inventories by the 118 patients in the study. The composite score was generated by dividing the number of these five symptoms with reported improvement for each enterade® usage group by the total number of reports of the five symptoms in that usage group. There was a 78% improvement, as shown by the composite score, for patients who used enterade® for >7 days (Figure 2F). The improvement from 7% to 47% was significant ($p < 0.05$), as was the improvement from 7% to 78% ($p < 0.05$) (Figure 2F).

The improvements in symptoms as a whole led us to also consider improvement for patients with one, two, or at least three symptoms at the time of receiving enterade®. No association between the number of initial symptoms and the degree of improvement was observed in the patients who consumed enterade® for 1-6 days ($p > 0.05$, Figure 3A). For the 103 patients who used the enterade® for > 7 days, the improvements observed for patients who initially reported multiple symptoms were significantly greater than those for patients who initially reported a single symptom ($p < 0.05$, Figure 3B). Indeed, whereas 61% of patients with a single symptom who used enterade® for > 7 days reported some improvement, the corresponding number for the patients with two or more symptoms was 98% (Figure 3B). Of the 41 patients with three or more symptoms who consumed enterade® for at least one day, 33 (80%) continued to use the product for at least seven days, a high degree of compliance.

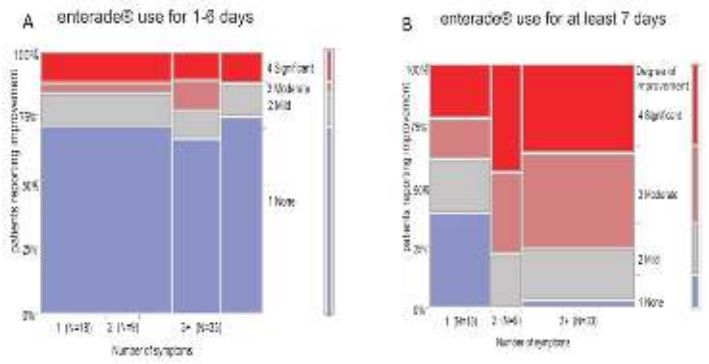

Figure 3: Mosaic plot for the proportion of patients reporting improvement, the degree of improvement and number of initial symptoms for the patients who consumed enterade® for 1-6 days (A) or for > 7 days (B). A greater proportion of the patients with at least three symptoms in the group consuming enterade® > 7 days reported improvement, and the row mean score test assessing relative level of improvement across the three symptom groups was statistically significant ($p = 0.0086$). A similar relationship was not observed for those consuming enterade® for 1-6 days ($p = 0.9435$).

Discussion

Despite the high prevalence of gastrointestinal symptoms observed in patients undergoing chemotherapy and radiation therapy, treatments are limited. In this retrospective feasibility analysis, we found that cancer patients with gastrointestinal complaints secondary to cancer therapy reported subjective improvement in a variety of symptoms following use of enterade®, an amino acid-based medical food, and that it appears that patients reported more improvement when consuming the product for at least seven days.

The improvements in diarrhea, nausea, dehydration and weight maintenance are directly or indirectly supported by pre-clinical studies. Irradiated mice treated with the amino acids in enterade® displayed improvements in electrolyte absorption, reduced macromolecular leakiness and bacterial translocation, and increased survival of cells in intestinal crypts and villi [13,14]. Weight and survival also increased in the irradiated mice following consumption of the amino acid mixture [14]. Furthermore, consumption of the amino acid mixture was associated with increased water consumption and decreased pica, a surrogate for nausea, in irradiated mice [16]. A case study of drastically improved immune therapy-induced diarrhea following treatment with enterade® is also consistent with analysis outcomes [15].

Around half of the patients were compliant with the recommendation to consume enterade® for at least seven days, a level higher than that seen in many studies [11]; the other half

chose to underuse (consuming for 1-6 days) or avoid using the product. Nausea associated with cancer therapy is notoriously difficult to manage, typically requiring multiple agents [11], and compliance is often problematic. Although the placebo effect cannot be ruled out, the reported improvements, particularly for self-reported diarrhea, nausea and dehydration, were remarkable. Anti-emetic drugs can successfully reduce acute vomiting but fail to effectively control nausea in 60-70% of patients [11].

Some confounding factors may have impacted outcomes or compliance in this study. The placebo effect and biased reporting of favorable outcomes cannot be ruled and could have impacted results, as this was not a randomized study. The major reported reason for underuse of enterade® was taste; 12 of the 58 patients who used enterade® for <7 days reported that they did not like the taste, as opposed to just 3 of the 60 patients who used enterade® for at least 7 days. Six patients discontinued the drink due to nausea, and others reported difficulty in obtaining the enterade® after the two-day trial supply. The majority gave no reason for discontinuation or underuse. However, management was identical for compliant and non-compliant patients, with traditional agents (e.g., loperamide and ondansetron) employed together with the enterade®, and all patients continued their anti-neoplastic therapy. The patients in the compliant group had a similar severity distribution of initial symptoms, a similar frequency of multiple symptoms, similar primary cancer distribution, and similar gastrointestinal symptom distribution compared to the poorly compliant groups. Finally, while our de novo composite score method requires further validation, results were consistent with classical individual symptom endpoints (e.g., diarrhea, dehydration, weight loss) (Figure 2).

In conclusion, these results suggest that an amino acid-based medical food may alleviate symptoms of gastrointestinal toxicity due to cancer therapy, including diarrhea, nausea and dehydration. The greatest benefits appear to be seen among patients with the greatest number of initial symptoms, and better results were seen in patients who utilized the intervention for at least seven days. Our findings, although interesting, suggest that a prospective clinical trial is warranted to substantiate the signal of improvement of gastrointestinal toxicity symptoms after drinking enterade®.

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Conflict of Interest

.L. Luque and S. Cheuvront are employees for Entrinsic Bioscience Inc. C. Mantz and S. Finkelstein have no conflicts to disclose. The institution did not receive any financial support for the execution of the study. The only support provided by Entrinsic Biosciences Inc. was by supplying enterade® to the institution at no charge. The publication of this manuscript will be funded by Entrinsic Bioscience Inc. Entrinsic Bioscience, Inc., was involved in manuscript approval and decision to publish.

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