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ORIGINAL ARTICLE

A phase II, randomized, double blind trial of calcium aluminosilicate clay versus placebo for the prevention of diarrhea in patients with metastatic colorectal cancer treated with irinotecan

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Abstract
Purpose Calcium aluminosilicate clay (CASAD) is a naturally occurring clay that serves as a cation exchange absorbent. We hypothesized that oral administration of CASAD would reduce the rate of grade 3/4 diarrhea associated with irinotecan use for metastatic colorectal cancer (CRC) by adsorbing the SN-38 metabolite.
Methods Patients receiving irinotecan-based chemotherapy were randomized equally between CASAD and placebo arms in this multicenter trial in order to assess differences in the proportions of patients with grade 3/4 diarrhea within 6 weeks. Additionally, we compared symptom severity between the two arms using the M.D. Anderson Symptom Inventory.
Results Between May 2009 and May 2012, 100 patients were enrolled. In evaluable patients, 7 of 43 (16 %) on the CASAD arm compared to 3 of 32 (9 %) on the placebo arm experienced grade 3/4 diarrhea (P=0.70). The rate of any diarrhea among all patients was similar (CASAD arm, 64 % vs. placebo arm, 70 %). The rate of study dropout was 14 % in the CASAD arm and 38 % in the placebo arm (P=0.01). No

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differences were found in symptom severity, individual symptom items, and in serious adverse events between the two arms.

Conclusion Compared to placebo, CASAD use was safe but ineffective in preventing diarrhea in metastatic CRC patients treated with irinotecan-containing chemotherapy regimens. There were no distinct signals in terms of patient symptoms between arms, but there was significantly more patient drop-out in the placebo arm. Future CASAD trials will focus on the active treatment of diarrhea.

Keywords Calcium aluminosilicate clay (CASAD) · Irinotecan · Diarrhea · Colorectal cancer

Introduction

Metastatic colorectal cancer (CRC) is one of the most common causes of cancer deaths in the USA annually, accounting for 9 % of all cancer deaths. It is estimated that 142,820 patients will be diagnosed with this condition in 2013, of which 50,380 will die [1]. While generally incurable, metastatic CRC is treatable with modern chemotherapies, including irinotecan, resulting in an overall survival improvement—that has historically been about 8–12 months—to around 24 months [2–9].

Irinotecan is usually well tolerated; however, one of its major dose-limiting effects is diarrhea, which can lead to dehydration, electrolyte imbalance, malnutrition, renal impairment, increased risk of sepsis, delays in cancer treatment, impaired quality of life, hospitalization, and sometimes death [4, 10–13]. If diarrhea is not controlled with traditional treatments such as loperamide, irinotecan may be discontinued [10, 14]. There are two main types of diarrhea in patients receiving irinotecan. Early-onset diarrhea is a cholinergic syndrome that usually occurs within 24 h of irinotecan infusion causing abdominal cramping, diaphoresis, and diarrhea. Atropine is effective as a treatment and for prevention of this syndrome [14, 15]. Late-onset diarrhea is a more common and serious syndrome that appears 24 h or more after the administration of irinotecan and may be due to the active metabolite SN-38 [14–17]. The extent of grade 3/4 diarrhea has varied in prior clinical trials from 14 to 47.5 %, depending upon the schedule of administration of irinotecan, and whether it is used in combination with other agents [5, 11–13, 18].

Irinotecan is converted by hepatic and peripheral carboxylesterase to SN-38, which is subsequently glucuronidated and then actively excreted by the liver to the bowel lumen via bile. The major route of elimination is fecal [19, 20]. Preclinical studies have shown that SN-38 is primarily responsible for direct enteric injury and damage to the mucosal lining [20, 21].

Calcium aluminosilicate clay (CASAD) is a hydrated sodium calcium aluminosilicate clay (HSCAS). HSCASs have been used in food additives to prevent caking in human and animal feeds and are considered safe in humans [22, 23]. They have also been used in aflatoxin mitigation to selectively absorb the toxin in the gastrointestinal tract of animals by binding a dicarbonyl group on the aflatoxin into the calcium rich interlayer of the HSCAS [22]. SN-38 shares a similar dicarbonyl group to aflatoxin [24, 25]. We hypothesized that HSCAS could bind SN-38 in a manner similar to aflatoxin, thus decreasing SN-38-induced enteric injury and reducing the toxic effects of this metabolite to the intestinal tract, which would result in preventing or reducing severe diarrhea in patients receiving irinotecan.

Diarrhea is also a common side effect of chemotherapies administered to dogs. In a clinical trial that studied dogs with severe intractable diarrhea due to anthracycline chemotherapy, HSCAS led to the resolution of symptoms in 58.8 % of the dogs with chemotherapy-associated diarrhea [26].

The primary objective of this trial was to compare the efficacy of CASAD relative to a placebo in reducing the incidence of grade 3/4 diarrhea (as measured by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria) in patients with metastatic colorectal cancer receiving irinotecan-based chemotherapy for 6 weeks. Our secondary objectives were to compare safety of the CASAD vs. placebo and to evaluate the change in patients' overall symptom severity between the two arms.

Methods

Participants

Eligible patients included men and women 18 years or older with a diagnosis of metastatic CRC (scheduled to receive irinotecan alone or in combination with 5-flourouracil, leucovorin, or other biologics including bevacizumab) who had been treated with any number of prior treatment regimens for metastatic disease. Eligibility criteria included the following: Eastern Cooperative Oncology Group performance status of ≤2; adequate bone marrow function as defined by ANC >1,000/μL, platelets >100,000/μL; and adequate organ function defined as creatinine clearance >35 ml/min by Cockroft-Gault, alkaline phosphatase ≤2.5 times the upper limit of normal (ULN), and AST (SGOT) and/or ALT (SGPT) <2.5×ULN—unless in the presence of liver metastasis, where <5×ULN maintained eligibility. Women of childbearing age required a negative urine pregnancy test; women of childbearing age and all men were required to agree to use adequate contraception. Patients could receive one prior dose of irinotecan during the current treatment regimen; if they had

received two or more, they could participate if given a 4-week washout period from irinotecan.

Exclusion criteria included patients with the following: known allergy to irinotecan, a known status of UGT1A1 homozygocity, Gilbert's disease, preexisting diarrhea >grade 1, pregnancy, neurological or psychiatric disorders that would impede giving consent or interfere with treatment, uncontrolled serious medical illness (such as uncontrolled congestive heart failure, uncontrolled hypertension or arrhythmia, active angina pectoris, or symptomatic heart disease NYHA class II or greater), serious uncontrolled infections, concurrent radiation therapy or administration within 4 weeks of treatment, and uncontrolled brain metastasis or patients whose current medication schedule would not permit a 2-h window between administration of CASAD and other scheduled medications. Initially, patients who had ostomies were excluded, but the study was amended to allow these as a significant number of patients were excluded with rectal cancer due to the presence of an ostomy. Patients were recruited from ambulatory clinics from community affiliates of the MD Anderson Cancer Center Community Oncology Research Base or from colorectal clinics at MD Anderson Cancer Center. The study was approved by the Institutional Review Board at all participating sites and registered on ClinicalTrials.gov as NCT00748215.

Study design

This was a phase II, randomized, double-blind, multicenter study. Patients who provided written informed consent were randomized on a 1:1 ratio between the two study arms: CASAD or placebo. Patients were stratified by concurrent chemotherapy with 5-flourouracil and/or biologic therapy vs. no concurrent therapy. Study participants who developed diarrhea received a standard of care anti-diarrheal therapy. CASAD/placebo were provided by Salient Pharmaceuticals. Each CASAD capsule contained 500 mg of the active compound and was taken as two tablets four times daily. The treatment was continued for 6 weeks or until any off-treatment criteria were met. Patients were considered off-study if (1) they developed grade 3 or higher diarrhea, (2) completed 6 weeks of randomized therapy (3) changed chemotherapy to exclude irinotecan, or (4) were non-compliant. After completing 6 weeks on treatment, all patients had the option of receiving open label CASAD for an additional 6 weeks, including those removed from the CASAD/placebo due to grade 3 diarrhea.

Assessments

At the time of enrollment or just prior, patients' symptoms were assessed using the MD Anderson Symptom Inventory (MDASI), which is a validated measure of patients' self-assessment of symptom frequency and interference with mood and activity-related domains [27]. MDASI assessments were obtained at weeks 3, 5, and 6. Patients also completed a baseline bowel/ostomy assessment and a daily ostomy/stool diary. The stool diary was reviewed at weeks 3, 5, and 6 and during physician visits. Concurrent meds were reviewed and demographics were obtained pre-enrollment. Patients whose treatment was discontinued were followed for 30 days from the study endpoint to monitor toxicities. Adverse events were stratified by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Versions 3.0 and 4.0 (For most patients, and especially for those enrolled after January 5, 2011, CTCAE Version 4 was used).

Statistical analysis

One hundred patients were randomized equally between CASAD and placebo arms in order to assess whether CASAD was efficacious in preventing grade 3/4 diarrhea. The proportion of patients with grade 3/4 diarrhea within 6 weeks for each arm was compared. We included Bayesian futility monitoring in the study, with a recommendation to stop the trial for futility if it became clear that CASAD was not better than placebo. Letting P_{exp} and $P_{placebo}$ be the true proportions of patients free of grade 3/4 diarrhea within 6 weeks for the CASAD and placebo arms, respectively, the trial would stop early if $\Pr(P_{exp}>P_{placebo}+0.15|\text{data})<0.02$, computed using Bayesian posterior probabilities based on a beta-binomial model with a uniform prior of beta (1,1) for P_{exp} and $P_{placebo}$. At the end of the study, 95 % posterior credible intervals (pCI) were computed for P_{exp} and $P_{placebo}$. CASAD would be declared superior to placebo if $\Pr(P_{exp}>P_{placebo}|\text{data})>0.95$. If the true proportions were $P_{exp}=0.95$ and $P_{placebo}=0.80$, then this would yield power of 75 % and a one-sided type I probability of 0.05. A similar beta-binomial model was used to monitor toxicity every 20 patients, with the trial stopping early for toxicity if $\Pr(p_{ToxExp}>p_{ToxPlacebo}|\text{data})>0.80$, where p_{ToxExp} and $p_{ToxPlacebo}$ denote the proportion of grade 3/4 toxicities within the first 6 weeks among patients on the CASAD and placebo arms, respectively.

Dropouts from the study were handled by the various analysis populations. For the intent-to-treat (ITT) full analysis, the fact that patients dropped out were ignored and we imputed their missing data as "no change." For the ITT measurable analysis, if patients had measurements, we analyzed them, regardless of how much treatment they received. If they did not take sufficient drug to be considered as "evaluable," they were dropped from the "evaluable" analyses.

Patient characteristics at enrollment were tabulated and compared between treatment arms using chi-square tests, with exact analysis for tests with small counts (fewer than five) in any category, except age, which was compared using a *t* test. The counts of patients with diarrhea were tabulated overall,

for grade 3/4, and within the first 6 weeks of treatment and compared between the treatment arms using the exact Pearson's chi-square test. To calculate symptom severity, the MDASI questionnaire was summed over the first 13 questions, specifically the symptom questions, for weeks 0 (baseline), 3, 5, and 6. To summarize the cumulative symptom burden in the patients, we computed the area under the curve (AUC) of the MDASI symptom score across the first 6 weeks and the adjusted AUC computed as the area under the change in MDASI symptom score from baseline over the first 6 weeks. Week 0 and the adjusted AUC were tested between the two groups with *t* tests and presented with 95 % confidence intervals.

Missing data on the MDASI were handled in two stages: First, if there was an off-study questionnaire, then the weeks on-study were calculated, and if they matched the needed missing week, the off-study questionnaire was used for the corresponding week. Next, any remaining missing scores were imputed as long as baseline and at least one other time point were available. Values missing between times were imputed by calculating a straight line between the surrounding existing information, and the value of the line at that time was used. If the missing information was the last or last two times, then the most recent available time was carried forward. To test for sensitivity, the results from only those patients with MDASI information from all four time points are also presented.

The adjusted area under the curve (AUC) was calculated by first subtracting the time 0 score from each time point. Then, the trapezoidal area between time 0 and 3, 3 and 5, and 5 and 6 was calculated and summed for a total adjusted AUC. An AUC of 0 would mean essentially no change from the baseline. A positive AUC would mean that the patient experienced an increase in symptom severity over time. The adjusted AUC was used to offset patients' baseline differences in MDASI symptoms present at enrollment.

Toxicity data were included for comparison if toxicities occurred on or after the day of randomization and were at least possibly attributable to the study drug. All toxicity attributions were presented per the attending physician's notes. Frequencies were presented in butterfly plots. Additionally, all gastrointestinal symptoms on or after the day of randomization were presented regardless of attribution. Analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC) as well as Parameter Solver and Inequality Calculator (freely available from https://biostatistics.mdanderson.org/SoftwareDownload/). The authors have no financial relationship with the organization that sponsored the research.

Results for this trial have been reported using the CONSORT 2010 guidelines for the reporting of randomized trials (http://www.consort-statement.org/), wherever applicable. The full trial protocol may be obtained by contacting the corresponding author.

Results

Patient characteristics

From May 2009 to May 2012, 100 patients were enrolled in the study, completing the planned enrollment at MD Anderson and its CCOP sites. Of 100 enrolled patients, 50 were randomized to the CASAD arm and 50 to the placebo arm (Fig. 1). Patients' baseline characteristics were similar between the two arms (Table 1). Five patients (including one in the CASAD arm and four in the placebo arm) never received study treatment after randomization. Most patients (88 % in each arm) received other chemotherapy or biological therapies in addition to irinotecan. Ninety-two percent of patients in the CASAD arm and 96 % in the placebo arm had received prior chemotherapy before enrolling in the study. Ten percent of the patients had ostomies in the CASAD arm vs. 12 % in the placebo arm. There were some apparent, but non-significant, baseline differences in the overall numbers of stools produced per day in the CASAD compared to those in the placebo arms, as well as for alternating constipation and diarrhea. In both cases, the placebo group had more regular bowel symptoms.

The trial continued to completion without stopping early for toxicity or futility, although it nearly stopped early for toxicity at the last interim analysis after 80 patients with $\Pr(P_{exp}>P_{placebo}+0.15|\text{data})=0.023$, close to the 0.02 cut point needed to stop the trial early, where P_{exp} is the proportion of patients free from grade 3/4 diarrhea for 6 weeks. Including only treated patients, there were 7/49 (14 %, 95 % pCI 7.2–26.7 %) patients in the CASAD arm vs. 3/46 (7 %, 95 % pCI 2.4–17.5 %) patients in the placebo arm with grade 3/4 diarrhea during the first 6 weeks (Table 2). From this, we computed $\Pr(P_{exp}>P_{placebo}|\text{data})=0.10$, which was less than 0.95, so we could not conclude CASAD was more efficacious than placebo for the primary endpoint. A Fisher's exact test comparing the two arms found similar results ($P=0.84$). The incidence of any grade diarrhea in the two arms was very similar, 32/49 (65 %, 95 % pCI 51.2–77.1 %) patients in the CASAD arm vs. 34/46 (74 %, 95 % pCI 59.7–84.4 %) in the placebo arm (Table 2).

Patients' symptom data is summarized in Table 3 which displays patients' baseline symptom severity and adjusted AUC analysis. Of the 100 patients randomized, only 91 had baseline MDASI symptom severity scores. Of these, only 59 patients had full data at weeks 3, 5, and 6. Imputation of data enabled calculation of the adjusted AUC for 71 patients. For an intent-to-treat type analysis, patients with baseline MDASI symptom severity scores who did not have enough information for imputation were assigned an adjusted AUC of 0.

The mean symptom severity score (at week 0) in the CASAD vs. the placebo arm was 28.6 vs. 22.6 for all patients with week 0 scores. The adjusted analysis subtracting the

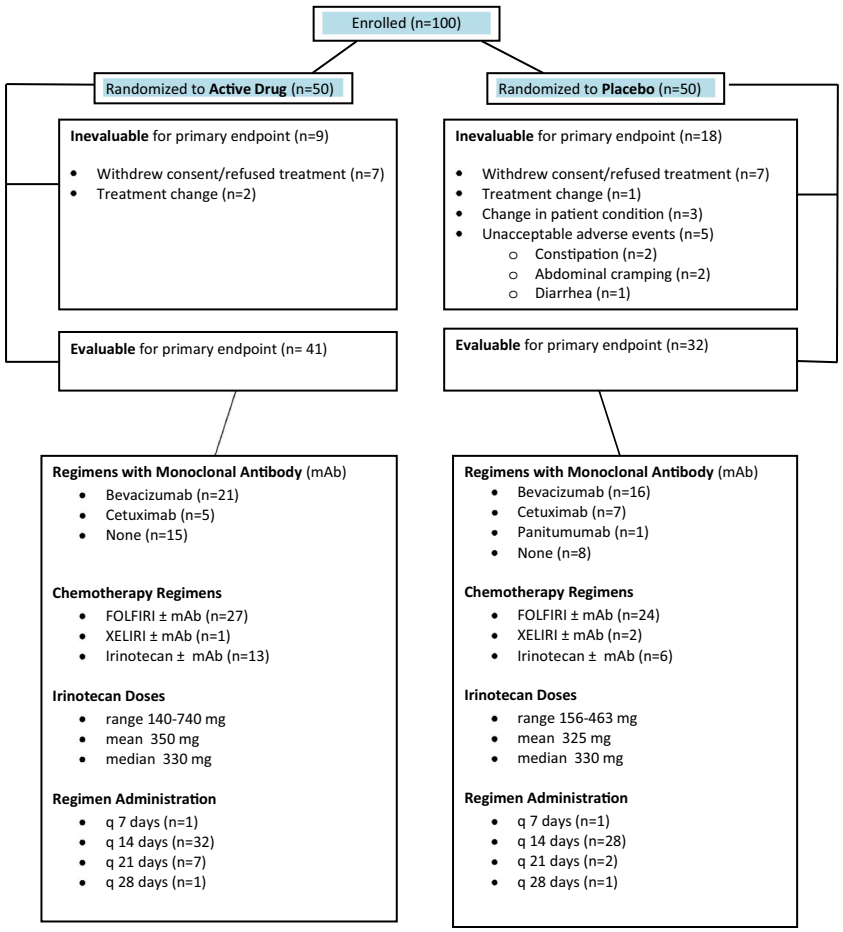

Fig. 1 Consort diagram. To be evaluable, patients needed to remain on study ≥5.5 weeks or have at least one episode of grade 3/4 diarrhea during the first 6 weeks after randomization

baseline score from each time point was considered to be the most appropriate way to compare the two groups because of this difference at baseline. For patients who had sufficient data for imputation, the adjusted AUC for CASAD vs. placebo was 10.3 vs. −1.4 (P=0.53). Similar results were seen in the subset of patients with complete data and also when including all patients with week 0 MDASI scores (substituting 0 for missing adjusted AUC values).

There was no apparent difference between the two groups in the proportion of patients experiencing gastrointestinal (GI) toxicities (Fig. 2a). In an evaluation of GI and non-GI toxicities, at least possibly attributable to the study drug, no apparent difference emerged between the two groups (Figs. 2b and 3). Interestingly, the rate of patient dropout from the study was higher in the placebo arm (38 %) vs. the CASAD arm (14 %) (P=0.01).

Discussion

While CASAD appeared to be safe, it was ineffective in preventing diarrhea in patients undergoing irinotecan-based chemotherapy in the treatment of metastatic CRC, and there were no trends to indicate benefit for the CASAD group. Importantly, there were no clinically relevant differences in the GI or non-GI toxicities that would seem to indicate any safety issues with CASAD. Interestingly, there was a significant difference between the study arms on the study dropout parameter, with more dropouts in the placebo arm. The reason for this discrepancy is not clear, possibly representing a chance result or some unmeasured characteristic of the placebo or CASAD that influenced dropout. Note that none of our results changed considerably among the intent-to-treat, imputed, or evaluable analysis groups, suggesting the results were robust to the dropouts.

Our hypothesis that CASAD would adsorb the SN-38 metabolite in the gut lumen and thus reduce diarrheal toxicity and associated symptoms was not supported by these data. The first possibility is that the CASAD does not bind SN-38 in the human gut as predicted by its chemical structure and preclinical models. We did not obtain any correlative specimens in order to determine whether such binding occurred. Another possibility is that CASAD binds the SN-38 in the gut, but the binding does not mitigate mucosal injury. The preclinical data related to our hypothesis was from mouse and rat

Table 1 Patient characteristics overall and by treatment arm

Characteristic	All patients *N* (%)	CASAD *N* (%)	Placebo *N* (%)	*P* value[b]
All patients	100 (100)	50 (100)	50 (100)	
Age in years—median (min–max)	57 (20–83)	56 (26–81)	61 (20–83)	0.49
Sex				0.42
Female	46 (46)	21 (42)	25 (50)	
Male	54 (54)	29 (58)	25 (50)	
Race/ethnicity				0.67
White/non-Hispanic	73 (73)	38 (76)	35 (70)	
White/Hispanic	10 (10)	4 (8)	6 (12)	
Black/non-Hispanic	16 (16)	7 (14)	9 (18)	
Asian/Hispanic	1 (1)	1 (2)	0 (0)	
Performance status				0.34
0	41 (41)	23 (46)	18 (36)	
1	52 (52)	22 (44)	30 (60)	
2	6 (6)	4 (8)	2 (4)	
Missing	1 (1)	1 (2)	0 (0)	
Baseline stools				0.46[a]
Less than 1 stool per day	10 (10)	7 (14)	3 (6)	
1–3 stools per day	61 (61)	27 (54)	34 (68)	
Greater than 3 stools per day	6 (6)	3 (6)	3 (6)	
Ostomy	10 (10)	6 (12)	4 (8)	
Change <2 times/day	3	2	1	
Change 2–3 times/day	5	2	3	
Change 4–6 times/day	2	2	0	
Missing	13 (13)	7 (14)	6 (12)	
Stool formation				0.21
Hard, difficult to pass	6 (6)	4 (8)	2 (4)	
Well-formed, easy to pass	58 (58)	26 (52)	32 (64)	
Semi-formed/loose	19 (19)	12 (24)	7 (14)	
Very loose and watery	2 (2)	0 (0)	2 (4)	
Missing	15 (15)	8 (16)	7 (14)	
Alternate constipation/diarrhea				0.08
No	64 (64)	28 (56)	36 (72)	
Yes, some	20 (20)	12 (24)	8 (16)	
Yes, significant	3 (3)	3 (6)	0 (0)	
Missing	13 (13)	7 (14)	6 (12)	
Prior therapies				0.72
None	1 (1)	0 (0)	1 (2)	
Surgery only	5 (5)	1 (2)	4 (8)	
Chemo only	2 (2)	1 (2)	1 (2)	
Surg + rad	1 (1)	0 (0)	1 (2)	
Surg + chemo	68 (68)	36 (72)	32 (64)	
Surg + rad + chemo	22 (22)	11 (22)	11 (22)	
Missing	1 (1)	1 (2)	0 (0)	

Surg surgery, *Rad* radiation therapy, *Chemo* chemotherapy

[a] The comparison is for distribution of stool count and ostomies only. It does not include subgroups under ostomy or missing values

[b] Patients with missing values for a characteristic are not included in the analysis

models [20, 21], and it may be that the microbiome specific to the human gut is important. Gut bacteria are responsible for the de-conjugation of SN-38 (via glucuronidase activity) and this may influence the expression of the mucosal injury. We

Table 2 Patients with diarrhea counts by treatment group and treatment status (N=100)

	CASAD		Placebo	
	Treated N (%)	Untreated N (%)	Treated N (%)	Untreated N (%)
All patients	49 (100)	1 (100)	46 (100)	4 (100)
Any diarrhea	32 (65)	0 (0)	34 (74)	1 (33)
Any diarrhea in first 6 weeks	27 (55)	0 (0)	26 (49)	0 (0)
Grade 3/4 diarrhea	8 (16)	0 (0)	5 (11)	0 (0)
Grade 3/4 diarrhea in first 6 weeks	7 (14)	0 (0)	3 (7)	0 (0)

Patients are classified as untreated if any of these occurred: they have no information entered in both study drug and drug diary or their study drug note indicates that no treatment was given

did not exclude probiotic use, which has become increasingly popular among patients due to emerging data about the potential utility of probiotics for chemoprevention [28] and treatment of diarrhea resulting from cancer treatment (especially radiotherapy) [29, 30]. Probiotics could influence the gut bacteria or have other mechanistic interaction with CASAD with regards to SN-38. A further possibility is that the CASAD could have slowed the gut transit time and thus kept SN-38 exposed to the gut mucosa longer, possibly counteracting any advantage from adsorption of the SN-38.

We formulated our mechanistic hypothesis based upon the experience in dogs that benefitted from CASAD for treatment of diarrhea after chemotherapy. The study in dogs, which was part of the preclinical data used to justify this trial, was limited in the sense that none of the dogs received irinotecan [26], and the setting was post-chemotherapy diarrhea rather than pre-chemotherapy CASAD exposure intended to prevent diarrhea. The biology related to prevention and treatment of diarrhea may be distinct based on the difference in inflammatory proteins and other factors. Moreover, dogs have a distinct microbiome and that may also be relevant to the manifestation of this particular toxicity.

Based on the existing literature, we expected to see 30 % or more patients with a serious grade of diarrhea [10]. However, we found serious diarrhea in only 10 of 75 evaluable patients (less than half the expected rate), which reduced the power involved in this trial. The improved rates of diarrhea may be due to better overall supportive care and the vigilance with which this problem was assessed and managed compared to earlier trials. Future attempts to prevent diarrhea due to irinotecan will need to account for this lower expected rate of diarrhea.

One of the limitations of the trial pertains to the accuracy of attribution of toxicities to the study drug. When a novel agent is used for symptom control in the context of chemotherapy, physicians may struggle in deciding how to judge toxicity attribution, particularly in their clinical notes. For example, while alopecia is presented in our results (Fig. 3) as possibly,

Table 3 Mean MDASI symptom severity at baseline and adjusted AUC

	CASAD Mean (95 % CI)	Placebo Mean (95 % CI)	Difference[a] Mean (95 % CI)	P value[a]
All patients[b] N=91	N=46	N=45		
Week 0 symptom severity	28.6 (21.6, 35.5)	22.6 (16.3, 29.0)	5.9 (−3.3, 15.2)	0.21
Adjusted[c] AUC for weeks 0, 3, 5, 6	9.2 (−13.7, 32.1)	−0.9 (−18.8, 17.0)	10.1 (−18.6, 38.8)	0.48
Imputed data N=71	N=41	N=30		
Week 0 symptom severity	27.5 (20.2, 34.8)	18.6 (12.1, 25.2)	8.9 (−1.2, 18.9)	0.07
Adjusted[c] AUC for weeks 0, 3, 5, 6	10.3 (−15.4, 36.1)	−1.4 (−28.8, 26.0)	11.7 (−25.8, 49.2)	0.53
Complete data N=59	N=37	N=22		
Week 0 symptom severity	27.2 (19.4, 35.0)	17.7 (10.4, 25.0)	9.5 (−1.0, 19.9)	0.07
Adjusted[c] AUC for weeks 0,3,5,6	7.1 (−21.0, 35.2)	−5.7 (−36.0, 24.7)	12.8 (−29.8, 55.3)	0.53

AUC area under the curve

[a] Due to substantial unequal variances between the groups, the Satterthwaite P values and confidence intervals are presented

[b] Refers to all patients with baseline MDASI scores

[c] Refers to the area under of the curve of the change from baseline. If negative, then the average change from baseline is a reduction. Similarly, if positive, then the average change from baseline is an increase. The higher the score, the more patients experienced symptoms

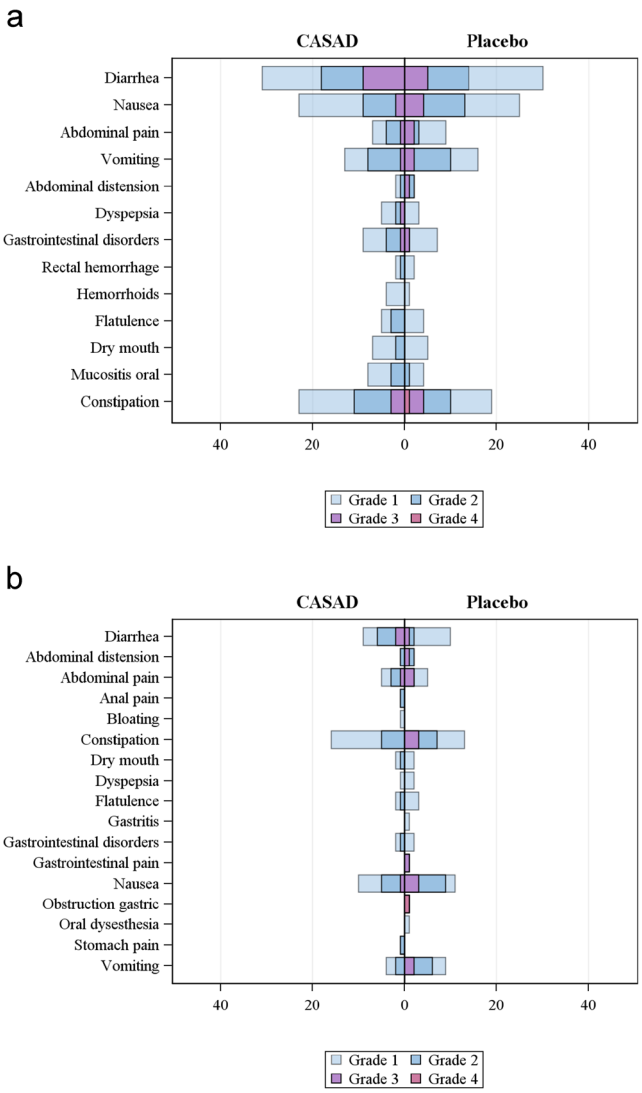

Fig. 2 Numbers of patients experiencing gastrointestinal toxicities. **a** presents toxicities with any relation to the study drug that occurred in at least three patients and **b** presents all toxicities that were classified as possibly, probably, or definitely related to study drug. *CASAD* calcium aluminosilicate clay

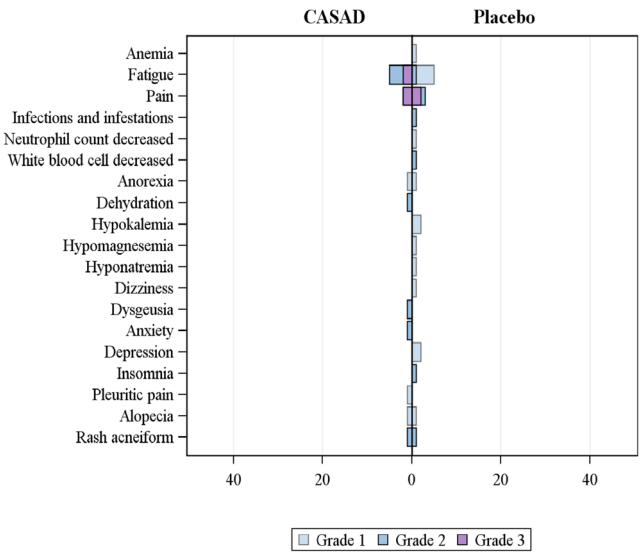

Fig. 3 Numbers of patients experiencing non-gastrointestinal toxicities. All toxicities that were classified as possibly, probably, or definitely related to study drug are included. *CASAD* calcium aluminosilicate clay

probably, or definitely related to the study drug, it is a known consequence of chemotherapy and most likely attributable to the same. Another limitation of this study is the absence of correlative science data to help us evaluate whether the CASAD actually adsorbed SN-38 as intended. The lack of efficacy could be due to inadequate adsorption of SN-38 or to the inadequate impact of SN-38 adsorption on the occurrence of diarrhea.

There remains no standard of care for prevention of irinotecan-related diarrhea or other cancer treatment-related diarrhea [30]. There have been various attempts to reduce diarrhea related to chemotherapy or chemotherapy and radiation including alkalizing the gastrointestinal tract with sodium bicarbonate [31], use of long-acting octreotide [32], and use of a peripherally acting enkephalinase inhibitor called racecadotril [33]. There have been other attempts at binding SN-38 in the intestine. Cholestyramine and levofloxacin were explored in a non-randomized trial and only 1 patient out of 51 developed grade 3+ diarrhea [34]. Another attempt at binding SN-38 was by the use of activated charcoal in an uncontrolled study of 28 patients [35]. Neither of these studies has been followed up with successful, controlled clinical trials.

In sum, severe diarrhea is a serious complication of irinotecan-based therapy, and a gap in our understanding of the pathophysiology of this problem and how to best prevent it remains. In the current trial, use of CASAD was safe, but it did not prevent diarrhea or improve the symptom experience of patients with metastatic CRC relative to placebo. Future trials related to diarrhea prevention are needed, particularly with attention to correlative endpoints that help elucidate the mechanisms of this toxicity as well as describe key patient-reported and clinical endpoints.

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