

Elobixibat Effectively Relieves Chronic Constipation in Patients with Cancer Regardless of the Amount of Food Intake

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Key Words. Cancer • Constipation • Elobixibat • Ileal bile acid transporter • Palliative care

ABSTRACT

Background. Constipation is a common, distressing complication in patients with cancer receiving palliative care. Elobixibat is a novel inhibitor of the ileal bile acid transporter that is used to treat chronic constipation by stimulating bowel function. However, its efficacy in patients with cancer has not been examined. This study investigated the drug's effectiveness in patients with cancer with chronic constipation.

Patients and Methods. This prospective-sampling, single-center, observational study included hospitalized patients with cancer diagnosed, using the Rome IV criteria, with chronic constipation. Within 2 weeks of hospitalization, each participant was administered elobixibat (5–15 mg) daily until discharge. Spontaneous bowel movements (SBMs), complete spontaneous bowel movements (CSBMs), Bristol stool form scale (BSFS) scores, and the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) scores were assessed before and after elobixibat

administration. We also evaluated the relationship between the amount of food consumed and the SBM frequency.

Results. Among the 83 participants, the mean pre- and post-treatment frequencies of daily SBMs were 0.3 and 1.2 ($p < .0001$) and those of CSBMs were 0.1 and 0.6 ($p < .0001$), respectively. The mean pretreatment BSFS score was 1.6, whereas the post-treatment value was 3.5 ($p < .0001$); the mean PAC-QOL score (overall) improved from 1.01 to 0.74 ($p = .01$). There was no significant change in the daily SBM frequency between fasting and feeding states (1.2 vs. 1.3; $p = .8$), and there was no correlation between the amount of food intake and the SBM frequency after elobixibat administration ($r = .03$). Serious adverse events were not observed.

Conclusion. This study showed that elobixibat is safe and effective for patients with cancer with chronic constipation, regardless of the food intake amount. *The Oncologist* 2021;26:e1862–e1869

Implications for Practice: Elobixibat was effective at relieving chronic constipation in patients with various cancers. Serious adverse events were not observed, and the relief of constipation was independent of variation in food intake.

INTRODUCTION

In Japan, the prevalence of chronic constipation is 2.6% for men and 4.9% for women, increasing with age for both sexes. Chronic constipation impairs patient quality of life

(QOL) and occurs in 32%–87% of patients with cancer receiving palliative care [1], causing extreme suffering and discomfort [2]. Chronic constipation in patients with cancer

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is due to multiple factors including decreased mobility, malnutrition, opioid analgesics and other drugs, and bowel obstruction [2]. In patients with cancer, opioids are often used to treat cancer pain, and opioid-induced constipation (OIC) occurs in 60%–90% of treated patients. Constipation also occurs as a side effect of chemotherapy. In Japan, magnesium oxide and stimulant laxatives have been widely used to treat chronic constipation. Furthermore, the laxatives lubiprostone (a selective chloride channel activator) and linaclotide (a guanylate cyclase C receptor agonist) were launched in 2012 and 2017, respectively. Naldemedine is a peripherally acting μ -opioid receptor antagonist that safely and effectively treats OIC [3].

Elobixibat, a novel inhibitor of the ileal bile acid transporter, is used to treat chronic constipation by increasing colonic bile acid concentrations and stimulating bowel function [4]. Elobixibat exerts its effect by increasing the bile acid concentration in the gut following food intake. However, patients with cancer often have decreased appetites, and the effect of elobixibat in this patient population has not been examined. Therefore, this study investigated the ability of elobixibat to relieve chronic constipation in patients with cancer who started taking the medication while hospitalized.

MATERIALS AND METHODS

Study Design

This prospective-sampling, single-center, observational study included patients from the Yokohama City University Hospital between July 2018 and April 2020. The study protocol complied with the Declaration of Helsinki [5] and Japan's Ministry of Health, Labour and Welfare's Ethics Guidelines for Clinical Research and was approved by the ethics committee of Yokohama City University Hospital (B171000027, November 8, 2017). Written informed consent for participation in the study was obtained from all participants. The trial was registered, on March 19, 2018, with the University Hospital Medical Information Network Clinical Trials Registry (UMIN 000031785).

Patient Eligibility Criteria

The study subjects were adult patients (20–85 years of age) with cancer, receiving palliative care and diagnosed with functional constipation according to the Rome IV criteria or already under treatment for chronic constipation. Chronic constipation was defined as constipation lasting >6 months and diagnosed using standard, symptom-based criteria. These criteria require that the patient experience fewer than three spontaneous bowel movements (SBMs) per week (defined as bowel movements occurring spontaneously and independent of rescue medication administered within the previous 24 hours), with at least one of the following symptoms occurring during $\geq 25\%$ of bowel movements: straining, lumpy or hard stools, or sensations of incomplete evacuation. Each diagnosis of functional constipation, according to the Rome IV criteria, was judged by an expert gastroenterologist. Regular use was defined as the use of a prescribed laxative at a fixed time of the day at

the discretion of the attending physician. Rescue use was defined as the use of a laxative at the patient's discretion, with or without the regular use laxatives. Patients were excluded if they were unable to take questionnaire surveys or keep defecation records.

Study Protocol

Within 2 weeks after study enrollment, prior to beginning elobixibat therapy, the patients kept records of their defecations (baseline, pretreatment period). Upon beginning therapy, the patients started taking regular daily doses of elobixibat (5–15 mg) and continued to record their daily bowel movements until discharged from the hospital (post-treatment period). SBMs, complete spontaneous bowel movements (CSBMs), Bristol stool form scale (BSFS) scores, and the Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL) scores were assessed before and after elobixibat administration. During the study, elobixibat doses were consistent, and the participants were allowed to continue taking other laxatives that they were previously given.

Defecation Record Analysis

During the baseline and treatment periods, patients were instructed to record their daily bowel habits. The SBM frequency was defined as the number of defecations per day without rescue laxative use within 24 hours. The responder to the elobixibat treatment was defined as SBM ≥ 0.43 /day (~ 3 per week) and ≥ 0.14 /day (~ 1 per week) increase from baseline SBMs. The frequency of CSBMs was defined as the number of defecations per days that were not accompanied by a sense of incomplete evacuation. Stool consistency was scored using the BSFS, which includes seven different categories used to evaluate the shape of stool as follows: type 1 and 2 indicating constipation; type 3 and 4 indicating normal defecation; and type 5, 6, and 7 indicating diarrhea [6]. The time to the first defecation was defined as the time (hours) between elobixibat administration and the first defecation.

The average amounts of the staples and side dishes, which were recorded in the medical record as a percentage, were extracted and used to assess if there was any relationship between the amount of food consumed and effects of elobixibat.

QOL Analysis

The PAC-QOL is a reliable, specific, self-administered questionnaire developed and validated to assess QOL impairment in patients with chronic constipation [7]. The PAC-QOL is translated into other languages, and this study used a Japanese version of the PAC-QOL (JPAC-QOL) [8]. This scale consists of 28 items evaluated using 5-point Likert scales (1, not at all; 2, slightly; 3, moderately; 4, quite a bit; 5, extremely or a great deal). The PAC-QOL score contains four subscales: physical discomfort, psychosocial discomfort, worries/concerns, and satisfaction. The overall score and each subscale score are expressed as average scores [7].

Table 1. Baseline characteristics of patients receiving elobixibat treatment

Parameter	Values
Number of patients	83
Sex, <i>n</i> (%)	
Male	49 (59)
Female	34 (41)
Age, average \pm SD, yr	70.4 \pm 13.5
Body mass index, mean \pm SD, kg/m ²	20.4 \pm 3.3
ECOG-PS, <i>n</i> (%)	
0	13 (16)
1	30 (36)
2	17 (20)
3	13 (16)
4	10 (12)
Average length of hospital stay, mean \pm SD, days	26 (14)
Number of patients with hospital stay, <i>n</i> (%) days	
\leq 14	10 (12)
15–28	48 (58)
29–84	25 (30)
Elobixibat dose, <i>n</i> (%)	
5 mg/10 mg/15 mg	13 (16)
10 mg	65 (78)
15 mg	5 (6)
Duration of elobixibat administration	
During hospitalization ^a , mean \pm SD, days	17 \pm 13
\leq 14, <i>n</i> (%)	53 (63)
15–28, <i>n</i> (%)	17 (20)
29–84, <i>n</i> (%)	
During hospitalization and outpatient follow-up ^b , mean \pm SD, days	91 \pm 113
\leq 56, <i>n</i> (%)	41 (49)
$>$ 56, <i>n</i> (%)	42 (51)
Laxative combination, <i>n</i> (%)	60 (72)
Number of regular use laxatives, <i>n</i> (%)	
0	23 (28)
1	35 (42)
2	13 (16)
3	9 (11)
4	2 (2)
5	1 (1)
The change in the regular use of other laxatives; numbers at the end of observational period <i>n</i> (%)	
Decrease	26 (31)
No change	52 (63)
Increase	5 (6)
Primary cancer site, <i>n</i> (%)	
Head and neck	16 (19)
Lung	7 (8)
Breast	1 (1)

(continued)

Table 1. (continued)

Parameter	Values
Gastrointestinal	16 (19)
Hepato-biliary-pancreatic	35 (42)
Genitourinary	3 (4)
Gynecologic	3 (4)
Other	2 (2)
Opioid use, <i>n</i> (%)	43 (52)
OMEDD \geq 60 mg/day	20
OMEDD $<$ 60 mg/day	23
Type of opioid, <i>n</i> (%)	
Morphine	13 (30)
Oxycodone	11 (26)
Fentanyl	2 (5)
Tapentadol	5 (12)
Tramadol	11 (26)
Others	1 (2)
Concurrent cancer treatment, <i>n</i> (%)	
Chemotherapy	23 (28)
Radiation	0 (0)
Chemoradiotherapy	15 (18)
Perioperative	1 (1)
Best supportive care	41 (49)
Other	3 (3)
Concomitant medications, <i>n</i> (%)	
Antacids	53 (64)
Antidepressants	18 (22)
Calcium antagonists	12 (28)
Parkinson's disease drugs	0 (0)
Past medical history	
Gastrointestinal surgery	35 (42)
Peritoneal dissemination	26 (31)
Ascites	24 (29)
Diabetes mellitus	23 (28)

^aPeriod between the start of administration during hospitalization and discharge.^bPeriod between the start of administration during hospitalization and the final prescription date in the outpatient follow-up.

Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group–performance status; OMEDD, oral morphine equivalent daily dose.

Statistical Analysis

The paired *t* test or Wilcoxon signed-rank test was performed to compare data within each group before and after the intervention. Binary variables were compared using the χ^2 test. In all cases, a *p* value $<$.05 was regarded as statistically significant. Analyses were performed using the JMP statistics program (version 15.0, SAS Institute, Cary, NC). Data are shown as means and SDs, unless otherwise stated. The differences among the three groups administered varying doses of elobixibat (5 mg, 10 mg, and 15 mg) were analyzed using one-way ANOVA; the F-test was used to calculate the *p* value. If the *p* value for the F-test was

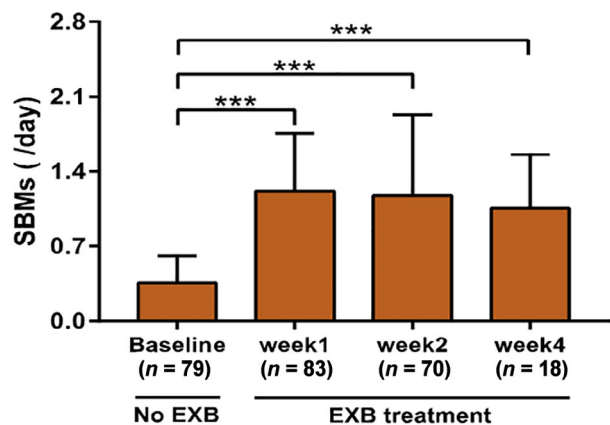


Figure 1. The clinical course of SBM frequency per day before and after elobixibat treatment. *** $p < .0001$. Abbreviations: EXB, elobixibat; SBM, spontaneous bowel movement.

significant at a two-sided significance level of 5%, then two-sample t tests were performed for all three pairwise comparisons across the three groups, using Fisher's least significant difference post hoc test, to adjust for multiple testing. The patients responding to treatment were also divided into two groups (remarkable effect group and normal effect group), according to the mean SBM frequency (SBM, 0.43 per day), and a univariate analysis was performed. We defined the value of after-before as Δ (Δ SBM, Δ CSBM, Δ BSFS, Δ JPAC-QOL); the SBM cutoff of 0.43 was defined as the median of Δ SBM (after SBM-before SBM) times per day, taking into account the bias in numbers. Thereafter, we focused on patient factors associated with a positive univariate analysis outcome ($p < .2$); a multivariate analysis was performed to determine the independent factors contributing to the remarkable effect.

RESULTS

Baseline Patient Characteristics

The baseline characteristics of the patients are shown in Table 1. We analyzed the results from 83 patients, including 49 men and 34 women, with an average age of 70.4 ± 13.5 years. The average length of hospital stay was 26 days. In addition, hospitalization within 14, 15–28, and 29–84 days accounted for 12%, 58%, and 30%, respectively. The average duration of elobixibat administration during hospitalization was 17 days. The average duration between the start of elobixibat administration during hospitalization and the final prescription during outpatient follow-up was 91 days. Sixty (72.3%) of the patients used other laxatives in combination with elobixibat. The number of regular laxatives used at the start of elobixibat treatment was 0, 1, 2, and > 3 in 28%, 42%, 16%, and 13% of the patients, respectively. The usage status of regular laxatives other than elobixibat at the end of the observation was as follows: in 31% of the patients, the dose was decreased, in 63%, the dose remained unchanged, and in 6%, the dose was increased. Among the 43 (52%) patients using opioids, morphine, oxycodone, fentanyl, tapentadol, and tramadol were used. The medical histories of the patients included

Table 2. Patient defecation status and quality of life score before and after elobixibat administration

Category	Before	After	p value
Number of patients	79	79	
SBM, number per day	0.3 (0.3)	1.2 (0.5)	$<.0001$
SBM responders, n (%)		72 (91%)	
CSBM, number per day	0.1 (0.2)	0.6 (0.2)	$<.0001$
BSFS	1.6 (0.1)	3.5 (0.9)	$<.0001$
First defecation time, hr		4.4 (2.7)	
Average of JPAC-QOL			
Overall	1.01 (0.7)	0.74 (0.6)	.01
Physical discomfort	0.94 (0.8)	0.65 (0.7)	.02
Psychosocial discomfort	0.83 (0.9)	0.48 (0.7)	.01
Worries/concerns	1.04 (1.0)	0.68 (0.9)	.03
Satisfaction	1.40 (0.8)	1.43 (0.8)	.9

Data are mean (SD) unless otherwise indicated.

Abbreviations: CSBM, complete spontaneous bowel movement; BSFS, Bristol stool form scale; JPAC-QOL, Japanese Patient Assessment of Constipation Quality of Life; SBM, spontaneous bowel movement.

gastrointestinal surgeries, peritoneal disseminations, ascites, and diabetes complications. The patients exhibited a range of primary cancer sites, including head and neck, lung, breast, gastrointestinal, hepato-biliary-pancreatic, genitourinary, and gynecologic. Furthermore, their treatments included chemotherapy, chemoradiotherapy, perioperative care, best supportive care, and others.

Elobixibat Effectiveness

Patient SBM daily frequencies (calculated as the weekly average) showed significant changes in weeks 1, 2, and 4, compared with baseline (Fig. 1). Comparing before and after treatment, the mean number of SBMs per day improved from 0.3 ± 0.3 to 1.2 ± 0.5 ($p < .001$), with 72 (91%) of patients demonstrating a response to treatment, as shown in Table 2. Furthermore, the mean number of CSBMs per day rose from 0.1 ± 0.2 to 0.6 ± 0.2 ($p < .001$), and the mean BSFS scores improved from 1.6 ± 0.1 to 3.5 ± 1.0 ($p < .001$). The first defecation occurred, on average, 4.4 hours after the initial elobixibat treatment. Overall, the JPAC-QOL scores also improved ($p = .01$), with the physical discomfort, psychosocial discomfort, and worries/concerns subscale scores showing significant improvements after elobixibat treatment (Table 2). Thus, elobixibat treatment resulted in significant improvements in the patients' defecation status and QOL. The status of the regular use and rescue use of other laxatives were also investigated, because they are associated with endpoints such as SBM and so on. At the end of the observation, the regular use of other laxatives decreased in 31%, remained unchanged in 63%, and increased in 6% of the patients. In addition, over time, in most cases with elobixibat administration, the number of other laxatives used remained unchanged or the dose was reduced (Table 1). Twenty-four patients used rescue laxatives during the observation period, and the average number of uses of rescue laxatives was two times per observational period (0.09 times

Table 3. Comparison between patients with effect and remarkable effect spontaneous bowel movement improvements

Variable	Remarkable effect group, n = 39	Effect group, n = 40	Univariate analysis, p value	Multivariate analysis	
				Odds ratio (95% CI)	p value
Male sex	19 (49)	27 (68)	.09	0.4 (0.1–1.4)	.2
Age, ≥65 yr	24 (62)	27 (68)	.6		
BMI, <18.5 kg/m ²	13 (33)	12 (30)	.8		
ECOG-PS 3–4 at admission	5 (13)	16 (41)	.004	0.2 (0.1–0.8)	.02
Dietary intake >50%	23 (59)	25 (63)	.8		
Tube feeding	2 (5)	13 (33)	.001	3.2 (0.4–28.3)	.3
Palliative care team support	16 (41)	25 (63)	.07	1.4 (0.3–5.5)	.7
Elobixibat dose of 10 or 15 mg	34 (87)	32 (80)	.4		
Elobixibat administration					
>28 days during hospitalization ^a	2 (5)	10 (25)	.01	0.3 (0.03–2.0)	.2
>56 days during hospitalization and outpatient follow-up ^b	17 (44)	24 (60)	.1	0.9(0.3–2.8)	.8
Fewer than 2 regular laxatives used					
None	12 (31)	12 (30)	.9		
Osmotic laxative	26 (67)	24 (60)	.5		
Stimulant laxative	10 (26)	9 (23)	.7		
Epithelial function-altering drug	5 (13)	4 (10)	.7		
Rectal osmotic laxative	0	0			
Naldemedine	6 (15)	7 (18)	.8		
Other	3 (8)	2 (5)	.6		
Cancer primary site					
Abdominal	7 (18)	20 (50)	.003	2.1(0.5–9.0)	.3
Opioid use	15 (38)	26 (65)	.018	0.8(0.2–2.9)	.8
Concurrent cancer treatment					
Best supportive care	20 (51)	20 (50)	.9		
Concomitant medication					
Antacids	23 (59)	27 (68)	.4		
Antidepressants	10 (26)	7 (18)	.4		
Calcium antagonists	5 (13)	7 (18)	.6		
Parkinson's disease drugs	0	0			
Past medical history					
Abdominal surgery	18 (46)	15 (38)	.4		
Peritoneal dissemination	16 (41)	10 (25)	.13	0.5(0.1–2.1)	.4
Ascites	13 (33)	11 (28)	.6		
Diabetes mellitus	9 (23)	13 (33)	.3		
Liver cirrhosis	1 (3)	2 (5)	.6		
Mental disorder	3 (8)	3 (8)	.97		

All data are presented as n (%) unless otherwise indicated.

^aElobixibat administration period between the start of administration during hospitalization and discharge.

^bElobixibat administration period between the start of administration during hospitalization and the final prescription date in the outpatient follow-up.

Abbreviations: BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group–performance status.

per day). Among the 24 patients, 20 patients used rescue laxatives that affected SBM, and the frequency of use was 1.7 times per observational period (0.07 times per day) (supplemental online Table 1). In addition, we evaluated the use of elobixibat, taking into account the dose administered. There was no significant difference in Δ SBM, Δ CSBM, Δ BSFS, and

Δ JPAC-QOL (overall and subscale) among the three treatment groups (5 mg, 10 mg, and 15 mg) (supplemental online Table 2). The number of cases administered 10 mg was 62; the number administered 5 mg was 13 cases; and the number administered 15 mg was 5. No difference in the background between these three groups was observed. Eastern

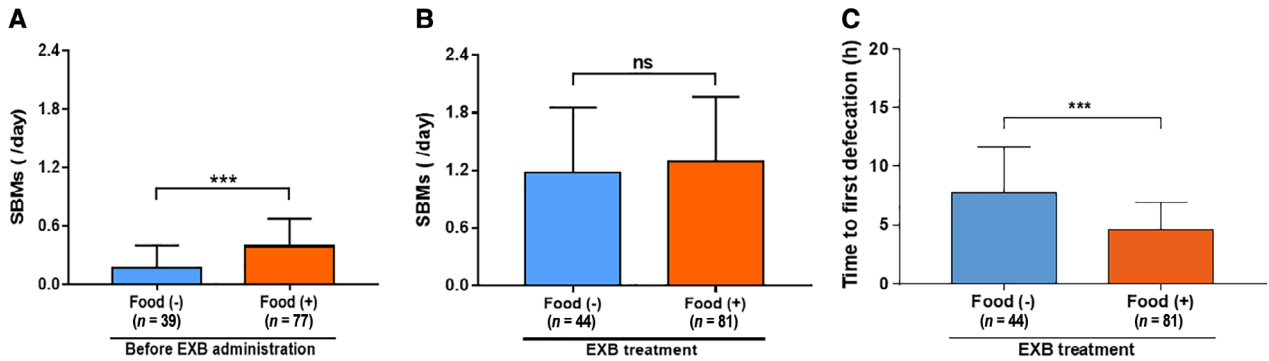


Figure 2. (A): Comparison of SBM frequencies between eating and fasting status before elobixibat administration. (B): Comparison of SBM frequencies between eating and fasting status after elobixibat administration. (C): Comparison of time to first defecation between eating and fasting status after elobixibat administration. Abbreviations: EXB, elobixibat; ns, not significant; SBM, spontaneous bowel movement.

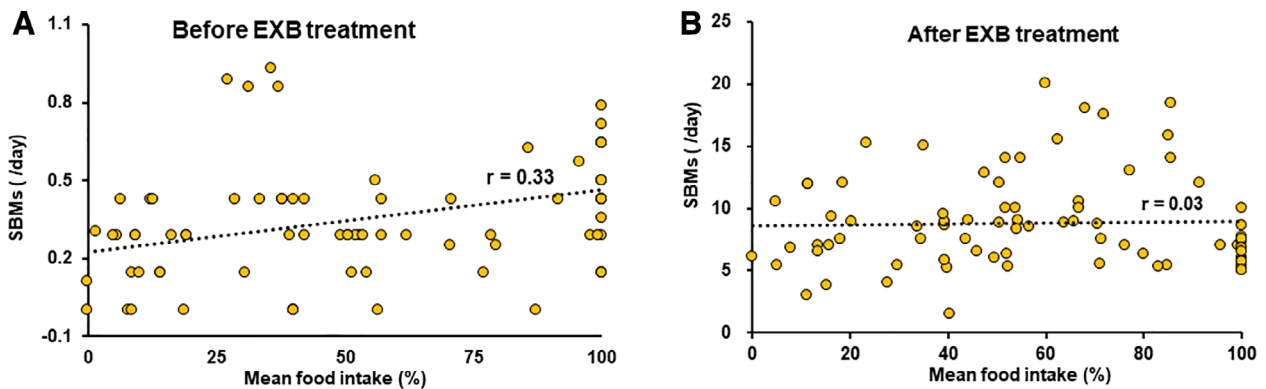


Figure 3. (A): Relationship between the amount of food intake and SBM frequencies before elobixibat administration. (B): Relationship between the amount of food intake and SBM frequencies after elobixibat administration. EXB; elobixibat. *** $p < .0001$.

Abbreviations: EXB, elobixibat; SBM, spontaneous bowel movement.

Cooperative Oncology Group–performance status (ECOG-PS) was significantly lower in 5 mg than that of the other groups. BSFS was also significantly higher in the 5 mg group (supplemental online Table 3).

Characteristics of the Elobixibat Remarkable Effect Group

The patients were divided into two groups, according to the mean change in SBM frequency (Δ SBM ≥ 0.43 per day; remarkable effect group [$n = 40$], Δ SBM < 0.43 /day; effect group [$n = 39$]), and the factors that showed a positive relationship ($p < .2$) in the univariate analysis were examined (sex, ECOG-PS, tube feeding, support of palliative care team, primary site of abdominal cancer, opioid use, and peritoneal dissemination). These factors were used in a multivariate analysis to determine the independent factors associated with the remarkable effect group. Admission ECOG-PS scores of 3 and 4 were associated with drug ineffectiveness group (odds ratio, 0.2; 95% confidence interval, 0.1–0.8; $p = .02$; Table 3).

Relationship Between Elobixibat and Food Intake

Prior to elobixibat administration, better SBM daily frequencies were observed when patients had food intake (0.39 per day) than when they were fasting (0.17 per day, $p < .0001$;

Fig. 2A), and the amount of food intake showed a mild correlation with SBM frequency ($r = 0.33$, Fig. 3A). However, SBM frequencies did not show a significant difference between the eating and fasting status (1.2 vs. 1.3 per day; $p = .5$; Fig. 2B) after elobixibat administration, and the amount of food consumed was not correlated with SBM frequency ($r = 0.03$, Fig. 3B). The time to the first defecation, after starting elobixibat treatment, was significantly longer when patients were fasting than when they had eaten (Fig. 2C).

Additionally, we focused on defecation status and QOL before and after elobixibat administration in subgroups after excluding patients who had at least one fasting period. The SBMs in weeks 1, 2, and 4 had significant changes compared with baseline (supplemental online Fig. 2); SBMs increased from 0.4 to 1.2 ($p < .0001$), SBMs response rate was 31 (86%), CSBMs increased from 0.2 to 0.6 ($p < .0001$), BSFS decreased 1.9 to 3.6 ($p = .01$), respectively. Overall, PAC-QOL scores also improved from 1.10 to 0.57 ($p = .0004$). The subscale of JPAC-QOL showed that psychosocial discomfort and worries/concerns after elobixibat treatment were greatly reduced compared with baseline (psychosocial discomfort: 0.94 vs. 0.30; $p = .0008$; worries/concerns: 1.14 vs. 0.39; $p = .0009$; supplemental online Table 4).

Table 4. Adverse events

Reason for cessation	Elobixibat cessation cases, n (%)
Serious adverse event	0
Adverse events	5 (6)
Abdominal pain	2 (2)
Diarrhea	1 (1)
Abdominal bloating	1 (1)
Nausea	1 (1)
Vomiting	0
Headache	0
Other	0
Oral intake difficulty	15 (18)
Patient refusal	1 (1)
Elobixibat cessation due to adverse events within 2 wk	5 (6)

Adverse Events

A total of 21 patients discontinued elobixibat administration during the study. The reasons for cessation included adverse events in five patients (6%) (abdominal pain, two; diarrhea, one; abdominal bloating, one; nausea, one), difficulty in oral intake (15 patients, 18%), and patient refusal (one patient, 1%). No serious adverse events were observed. Adverse events are shown in Table 4.

DISCUSSION

Previous studies reported 5–15 mg elobixibat administration improved SBMs, CSBMs, and JPAC-QOL scores in patients with chronic constipation [9–11]. Similarly, our study demonstrated that elobixibat treatment was safe and effectively relieved chronic constipation in hospitalized patients with cancer. In addition, the use of other laxatives and the use of rescue laxatives could affect the endpoints, such as SBM. The use of other laxatives increased in less than 10% of the patients, and therefore, it is unlikely that the increase in SBM is because of the increase in the use of other regular laxatives. The effect of the use of rescue laxatives on SBM is 1.7 times per observation period (0.07 times per day), and the effect on the endpoints is negligible. Our results did not indicate a dose-dependent variation in the response to elobixibat; however, the background (ECOG-PS and stool form) varied, the number of cases was less in the 5-mg and 15-mg groups, and the number of cases was biased. Therefore, the variations could be attributed to the lack of power.

According to the European Medicines Agency guidelines, patient defecation habits (QOL) are as important as defecation frequency (SBMs) in evaluating constipation treatment [12]. Although elobixibat (10 or 15 mg/day) showed significant CSBM improvements in patients without cancer with chronic constipation [9, 10], our study also demonstrated CSBM and JPAC-QOL improvements in patients with cancer within a short period (2 weeks) of starting elobixibat administration.

Bile acids are made in the liver and reabsorbed into the blood in the intestinal tract. In general, elobixibat exerts its effect by blocking bile acid reabsorption following its stimulated release in conjunction with food intake. Interestingly, in this study, SBM frequencies improved following elobixibat administration in patients with cancer with and without food intake. However, patients without food intake showed a significantly prolonged period between drug administration and the first defecation, compared with those consuming food. In previous reports, serum bile acid levels increased with food intake, but bile acid secretion was also observed when the stomach was empty [13, 14]. Thus, elobixibat's effect may have been observed because endogenous bile acids were secreted when patients were fasting [13].

In our study, the SBM nonresponder group was characterized by an ECOG-PS >3. Previous reports indicated that lower exercise frequencies were associated with a higher prevalence of constipation [15]. Performance status may be an important index causing severe constipation in patients with cancer.

The reason for discontinuation was mainly because of oral food intake difficulties rather than adverse events; this was considered to be a peculiarity associated with patients with cancer. As we found no significant difference in SBM frequencies when patients with cancer had fasted or not after elobixibat administration, continuous administration of elobixibat may be considered when patients have difficulties in oral food intake.

The strengths of the present study include its examination of patients with cancer in a hospital setting, its comparison of food intake among the participants, the prospective-sampling design, and the evaluation of defecation QOL. Conversely, the study's limitations include a degree of selection bias because of the study involving only a single center, the short duration of the study, the fact that it had an observational design, and the absence of bile acid measurements. Further studies, involving multiple centers and a long-term, randomized control design are warranted.

CONCLUSION

This is the first study to demonstrate the safety and effectiveness of elobixibat for relieving chronic constipation in patients with cancer. Elobixibat was found to be effective regardless of the amount of food consumed by the patient. However, further evidence is needed to confirm these results in patients with cancer.

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DISCLOSURES

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