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Real-world data of anamorelin in advanced gastrointestinal cancer patients with cancer cachexia

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Abstract

Background Cancer cachexia is characterized by the loss of body weight (BW) and anorexia. Anamorelin (ANAM) is a selective ghrelin receptor agonist with appetite-enhancing anabolic action. The ONO-7643-05 trial demonstrated that ANAM increased lean body mass and improved anorexia in a Japanese population. However, the clinical outcomes of patients on ANAM have not yet been reported.

Patients and methods We investigated the clinical outcomes of patients with unresectable, advanced, or recurrent gastrointestinal cancer (colorectal, gastric, or pancreatic cancer) who were treated with ANAM between April 2017 and August 2022. Cachexia was defined as the presence of anorexia and a loss of $\geq 5\%$ of BW within 6 months. To evaluate the response to ANAM, the patients who had discontinued ANAM within 3 weeks were excluded. Response to ANAM was defined as maintenance of or increase in BW and improved appetite from baseline at every 3-week evaluation. We also collected data on the reasons for the discontinuation of ANAM and the correlation between clinical factors and ANAM response. Safety analysis of ANAM was performed for all patients who received ANAM.

Results Seventy-four patients were included in this study (49 males and 25 females), with a median age of 67.1 years (range, 36–83). The primary tumors were colorectal cancer in 27 (36.5%), gastric cancer in 20 (27.0%), and pancreatic cancer in 27 (36.5%). The Eastern Cooperative Oncology Group performance status was 0 in 10 (13.5%), 1 in 44 (59.5%), and ≥ 2 in 20 (27.0%). The number of previous chemotherapy regimens was 0 in 20 (27.0%), 1 in 22 (29.7%), and ≥ 2 in 32 (43.2%). ANAM was discontinued within 3 weeks in 28 patients for the following reasons: low-grade (grade 1 or 2) adverse events in 15 patients, ileus in three, grade 3 fatigue in one, progressive disease in one, censored follow-up in six, and unknown reasons in three. The proportion of ANAM responders was 63.6% (95% confidence interval, 47.8–77.6%). Among baseline characteristics, age ≥ 75 attenuated the ANAM response ($p = 0.03$). ANAM responders showed better disease control with chemotherapy than non-responders (75.0% vs. 37.5%, $p = 0.02$).

Conclusions ANAM may improve the outcomes of patients with gastrointestinal cancer cachexia in clinical practice.

Keywords Anamorelin, Anorexia, Body weight, Cachexia, Gastrointestinal cancer, Body weight loss

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Background

Cancer cachexia is a complex malnutrition syndrome characterized by significant weight loss, primarily due to skeletal muscle loss and progressive functional disability, a condition that is difficult to correct with nutritional therapy alone [1]. Inflammatory cytokines [2–4], proteolysis-inducing factors [5], and lipid-mobilizing factors [6] produced by the tumor or host immune response play a major role in the development of cancer cachexia. Cancer cachexia is a complication that occurs in up to 80% of patients with advanced cancer and is estimated to account for 20% of cancer deaths [7–9]. Cancer cachexia has also been reported to increase the side effects of chemotherapy [10] and worsen the quality of life [10, 11] and prognosis [2, 12].

Patients with gastrointestinal cancers, such as pancreatic, gastric, and esophageal cancers are prone to cachexia [13, 14, 15]. However, no safe and effective treatments have been widely approved, and many countries rely on treatments such as megestrol acetate, which carries a high risk of thrombotic events and has limited utility. The ONO-7643-05 study showed that anamorelin (ANAM), a selective ghrelin receptor agonist, increases lean body mass and improves anorexia in patients with gastrointestinal cancer with cachexia [16]. Based on these results, ANAM has received regulatory approval in Japan for the treatment of cachexia in patients with gastrointestinal cancer. However, the patients enrolled in this study were in relatively good general condition with preserved organ function, and 80% of them had colorectal cancer (CRC). In clinical practice, because cancer patients with cachexia are often in poor general condition and a large proportion of them have pancreatic or gastric cancer, the actual status and usefulness of ANAM for gastrointestinal cancer in clinical practice are not clear.

In this study, we retrospectively evaluated the compliance, efficacy, safety, and predictors of ANAM efficacy in patients with gastrointestinal cancer, including those with poor general conditions, in real-world practice.

Methods

Patients and procedures

In this study, we selected patients with unresectable, advanced, or recurrent CRC; gastric cancer; and pancreatic cancer who underwent chemotherapy and received ANAM for cachexia at the Shizuoka Cancer Center between April 2017 and August 2022. Patients were administered ANAM (100 mg) once daily for 12 weeks. Patients who responded to the ANAM treatment continued to receive ANAM beyond the initial 12-week period. Cachexia was defined as follows: involuntary body weight loss $\geq 5\%$ within the last 6 months, presence of anorexia, and meeting at least two of the following criteria: fatigue, malaise, and generalized muscle weakness.

At least one of the following conditions also had to be met: albumin < 3.2 g/dL, C-reactive protein > 0.5 mg/dL, and hemoglobin level < 12 g/dL. Patients receiving best supportive care (BSC) and those with missing weight data were excluded from the analysis. This study was approved by the Institutional Review Committee of the Shizuoka Cancer Center (Shizuoka, Japan) (Approval No. J2022-136-2022-1-3) and the principles outlined in the Declaration of Helsinki. All participating patients were provided full details of the study, and the opt-out policy was disclosed.

Evaluation

All clinical data were retrospectively obtained from the medical records during the ANAM administration period. The following parameters were collected and analyzed: sex, age, Eastern Cooperative Oncology Group performance status (ECOG PS), body weight, blood test results, tumor type, disease status, number of previous treatment regimens, and history of gastric surgery. Because gastrectomy produces a decrease in ghrelin secretion, we added a history of gastric resection to the background factors to account for its effect. In this study, we defined ANAM responders as patients who maintained or gained body weight (≥ 0 kg) during the 3-weekly assessments and reported an improvement in appetite. Body weight was measured between each 3 weeks' time point following the initiation of ANAM administration and the maximum value between each time point was used. The patients who received at least one dose of ANAM were included in the safety analysis, and those who discontinued ANAM within 3 weeks were excluded from the efficacy analysis. To evaluate the relationship between disease status and ANAM treatment efficacy, disease control was defined as the absence of progressive disease by RECIST version 1.1 [17] evaluation at the imaging examination immediately preceding the 3-weekly evaluation point. Treatment-related adverse events were determined using the National Cancer Center Institutional Common Terminology Criteria for Adverse Events, version 5.0 [18].

Statistical analysis

The statistical significance of the differences in weight change during ANAM administration between ANAM responders and non-responders was examined using the Mann–Whitney U test. The predictive factors for ANAM responders were investigated using Fisher's exact test. Furthermore, we hypothesized that the ANAM response is associated with disease control in primary disease. Using Fisher's exact test, we evaluated the association between ANAM response and RECIST evaluation by CT, most recently after ANAM administration. Statistical analyses were performed using EZR, version

1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) [19]. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Eighty-nine patients with gastrointestinal cancer and cachexia were administered ANAM. Among them, 15 patients received BSC. Of the 74 patients treated with ANAM and palliative chemotherapy, 28 discontinued ANAM within 3 weeks, and two had missing body weight data. Consequently, 44 patients were included in the efficacy analysis (Fig. 1).

Patient characteristics are shown in Table 1. The sample included 25 females (33.8%) and 49 males (66.2%), with a median age of 67.1 years (range, 36–82 years) and median body weight of 51.2 kg (30.7–75.6 kg). The primary tumors included colorectal cancer in 27 (36.5%), pancreatic cancer in 27 (36.5%), and gastric cancer in 20 (27.0%). Approximately half of the patients (56.7%) had fewer than two prior treatment regimens. Of the nine patients (20.5%) with a history of gastric surgery, total gastrectomy was performed in five (11.4%), distal gastrectomy, in three (6.8%), and pancreaticoduodenectomy, in one (2.3%). The number of treatment regimen lines overall and by primary tumor at the administration of ANAM is shown in Fig. 2. Patients with gastric and pancreatic cancers on early-line chemotherapy (first or second-line regimens) were more likely to receive ANAM than those with other types of cancers.

Efficacy of anamorelin

In the efficacy analysis, ANAM treatment resulted in the maintenance or increase in body weight from baseline and improvement in appetite in 28 of 44 patients. The ANAM response rate was 63.6% (95% confidence interval [CI], 48.8–77.6%). The changes in mean body weight from baseline to week 12 are shown in Fig. 3. There were no significant differences in the mean changes in body weight between ANAM responders and non-responders at each 3-weekly assessment. The baseline characteristics of ANAM responders and non-responders are shown in Table 2. The number of ANAM responders was significantly lower in the group older than 75 years. The distribution of the time points of maximum weight gain for each primary tumor site in the 28 ANAM responders is shown in Fig. 4. Most of the patients with gastric and pancreatic cancers showed maximum body weight gain within 6 weeks, whereas most of the patients with CRC showed maximum body weight gain after 9 weeks. Of the 28 ANAM responders, 10 showed maximum weight gain at week 3, seven, at week 6, two, at week 9, and nine, at or after week 12.

Reasons for discontinuation of anamorelin

In this study, 28 patients discontinued ANAM treatment within 3 weeks. The reasons for discontinuation were as follows: 15 patients had low-grade (grade 1 or 2) adverse events (AEs), two had ileus, one had grade 3 fatigue, one had progressive disease, six had censored follow-up, and three had unknown reasons. Among the 15 patients with low-grade adverse events, four had grade 1 fatigue, four

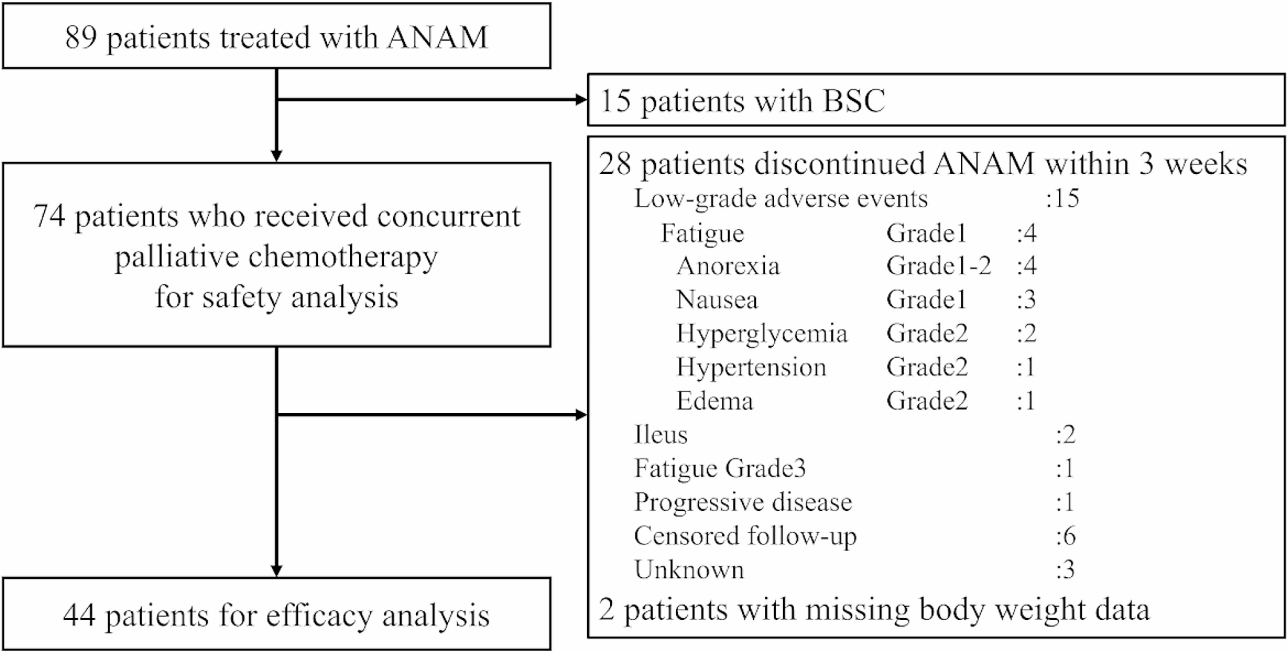


Fig. 1 Patient selection criteria. A flow chart illustrating the composition of the study cohort. ANAM: anamorelin, BSC: best supportive care

Table 1 Patient characteristics at baseline

	ANAM 100 mg (n = 74)
Sex, no. (%)	
Male	49 (66.2)
Female	25 (33.8)
Age: Median [range], year	67.1 [36–83]
Weight Median [range], kg	51.2 [30.7–75.6]
BMI: median [range], kg/m ²	19.2 [13.1–28.2]
ECOG PS, no. (%)	
0	10 (13.5)
1	44 (59.5)
≥ 2	20 (27.0)
Body weight loss, no. (%)	
5–10%	45 (60.8)
> 10%	29 (39.2)
Albumin (g/dL), no. (%)	
≥ 3.2	54 (73.0)
< 3.2	27 (36.5)
CRP (mg/dL), no. (%)	
≥ 0.5	32 (43.2)
> 0.5	42 (56.8)
Hemoglobin (g/dL), no. (%)	
≥ 12.0	17 (23.0)
< 12.0	57 (77.0)
Tumor type, no. (%)	
Colorectal	27 (36.5)
Gastric	20 (27.0)
Pancreatic	27 (36.5)
Disease status, no. (%)	
Locally advanced unresectable	13 (17.6)
Metastatic	36 (48.6)
Recurrence after surgery	25 (33.8)
No. of previous treatment regimens, no. (%)	
0	20 (27.0)
1	22 (29.7)
≥ 2	32 (43.2)
History of Gastric surgery, no. (%)	
Total gastrectomy	5 (6.8)
Distal gastrectomy	6 (8.1)
Pancreaticoduodenectomy	3 (4.1)

ANAM, anamorelin; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status

had grade 1 or 2 anorexia, three had grade 1 nausea, two had grade 2 hyperglycemia, one had grade 2 hypertension, and one had grade 2 edema. Of the 44 patients who were treated with ANAM for ≥ 3 weeks, 21 (47.7%) discontinued ANAM, and 18 (40.9%) were still on ANAM therapy for ≥ 12 weeks. The most common reasons for discontinuing ANAM were decreased oral intake (20.5%) and hyperglycemia (13.6%).

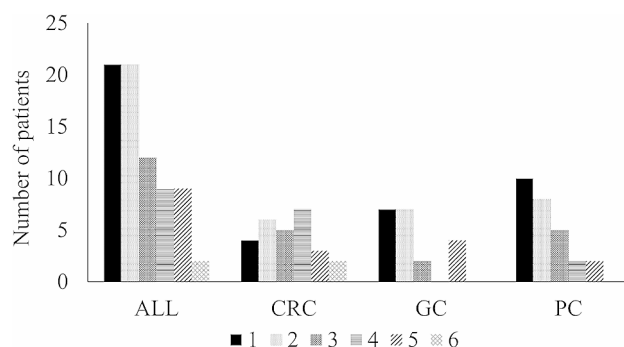


Fig. 2 The number of treatment regimen lines overall and by primary tumor at the administration of anamorelin. CRC: colorectal cancer, GC: gastric cancer, PC: pancreatic cancer

Relationship between disease control and anamorelin efficacy

The relationship between disease control and ANAM efficacy is shown in Table 3. Among the 28 patients who responded to ANAM, 21 (75.0%) achieved disease control. In contrast, of the 16 patients who did not respond to ANAM, six (37.5%) achieved disease control. The odds ratio obtained on comparing these two groups was 4.80 (95% CI: 1.11–23.20), indicating that significantly more patients who responded to ANAM achieved disease control than those who did not.

Treatment-related adverse events

Treatment-related AEs were observed in 54.1% of the patients: 4.0% AEs were classified as severe, and 6.8% AEs led to discontinuation. The most common (≥ 5%) AEs included hyperglycemia (13.5%), fatigue (12.2%), nausea (6.7%), and stomach pain (5.3%) (Table 4). Regarding severe AEs, two patients had grade 3 hyperglycemia, both of whom had preexisting diabetes at the initiation of ANAM administration.

For the 10 patients who developed hyperglycemia, background factors are shown in Table 5. Of the 10 patients, six had pancreatic cancer, three had gastric cancer, and one had CRC. Hyperglycemia occurred in 22.2% of patients with pancreatic cancer, 15.6% of patients with gastric cancer, and 3.7% of patients with CRC. All patients with pancreatic cancer had impaired glucose tolerance or diabetes mellitus, and grade 3 hyperglycemia was observed in pancreatic cancer patients. Two patients discontinued treatment within 3 weeks due to hyperglycemia, and three of the remaining 8 patients responded to ANAM.

Discussion

This study evaluated the real-world treatment course, efficacy, and safety of ANAM for a range of gastrointestinal cancers, including gastric, pancreatic, and colorectal cancers.

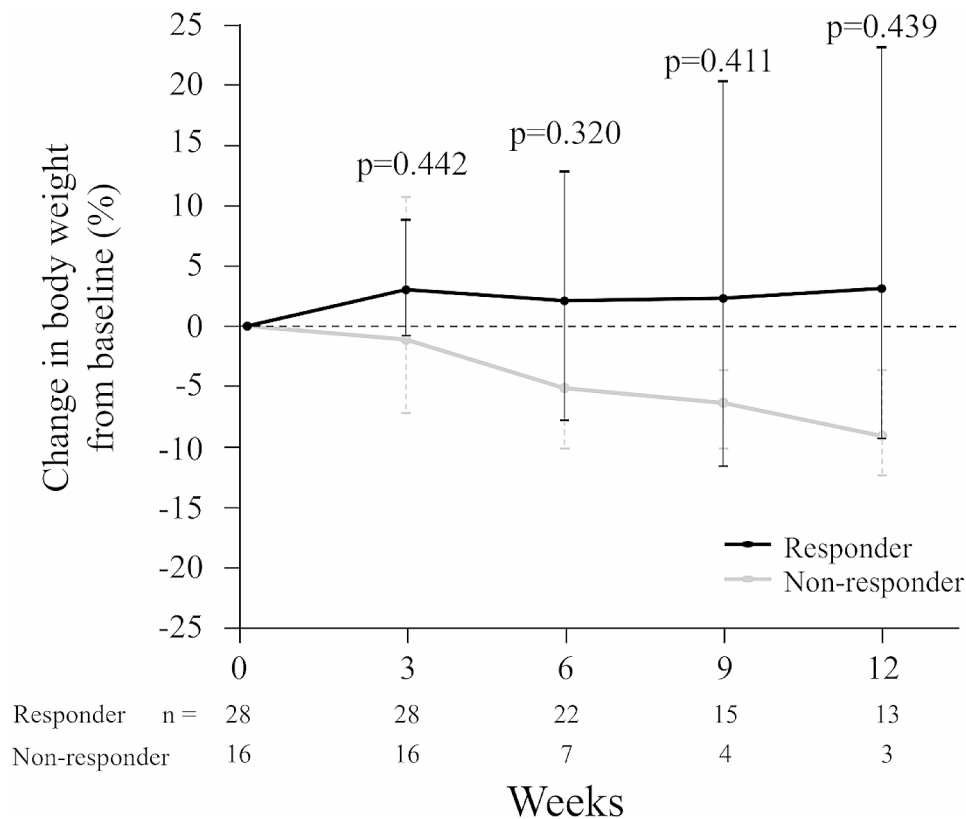


Fig. 3 The changes in mean body weight from baseline to week 12. Error bars represent 95% Confidence Interval

Patients with gastric and pancreatic cancer together accounted for 64% of the total sample, and patients with poor condition of ECOG PS2 or higher accounted for 27%, which was higher than the proportion reported in the ONO-7643-05 trial [16]. Overall, the most common chemotherapy regimen for ANAM administration was an early line of two or fewer regimens. However, the early line was commonly administered to patients with pancreatic and gastric cancers, reflecting the differences in the timing of cachexia onset according to the cancer type. Namikawa et al. reported that half of gastric cancer patients had cancer cachexia within 6 months of starting chemotherapy and that patients with cachexia had a significantly worse prognosis than those without cachexia [20]. This may be because absorption disorders are more likely to occur in advanced gastric cancer [21]. One study reported that 32% of patients with pancreatic cancer developed cancer cachexia within the first 12 weeks of anticancer therapy [22]. The high frequency of cachexia in pancreatic cancer can be attributed to the fact that cell signaling through KRAS mutations, which are highly prevalent in pancreatic cancer, promotes skeletal muscle protein degradation and lipolysis, and that cancer impairs exocrine and endocrine functions of the pancreas, resulting in nutrient malabsorption [23]. Therefore, since cancer cachexia is recognized relatively early in patients with

gastric and pancreatic cancer, it is important to weigh patients from the start of chemotherapy and monitor cancer cachexia.

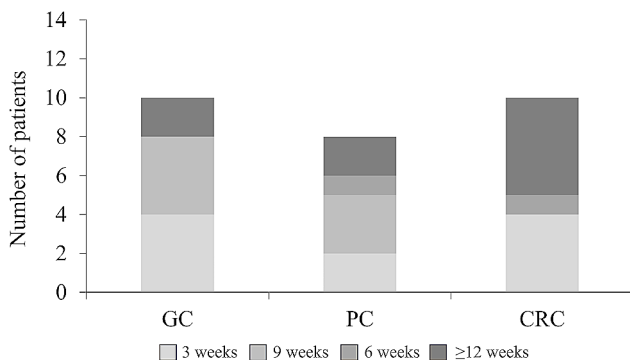
In the ONO-7643-05 trial, 89.9% of the patients were able to receive ANAM for more than 3 weeks; however, 37.8% of the patients discontinued within 3 weeks, primarily due to low-grade AEs. However, retrospectively, many of these AEs were manageable with supportive care. For example, although elevated blood glucose level is a common AE associated with ANAM, the study included patients who continued ANAM with an oral hypoglycemic agent. Therefore, even if low-grade adverse events occur, it may be possible to obtain benefits if ANAM is continued with appropriate management.

In this study, the ANAM response rate was 63.6% in the group that could receive ANAM for at least 3 weeks, similar to the 63.3% ANAM response rate in the ONO-7643-05 study. In the ONO-7643-05 trial, ANAM efficacy was defined as the maintenance of or increase in lean body weight. In contrast, in this study, efficacy was defined as maintenance or increase in body weight and improvement in anorexia. Efficacy analysis showed no significant differences in body weight at the 3-week intervals. This could be attributed to the fact that some non-responders who did not increase their appetite included patients who maintained or gained weight. However, after accounting

Table 2 Relationship between anamorelin responder and baseline characteristics ($n = 44$)

Characteristics		Responder ($n = 28$)	Non-responder ($n = 16$)	Odds ratio	p -value*
Sex	female	9 (33.3)	6 (37.5)	0.79	0.48
	male	19 (66.7)	10 (62.5)		
Age (year)	< 75	22 (78.6)	7 (43.8)	4.71	0.03
	≥ 75	6 (21.4)	9 (56.3)		
ECOG PS	0–1	21 (75.0)	14 (87.5)	0.43	0.45
	≥ 2	7 (25.0)	2 (12.5)		
Albumin (g/dL)	≥ 3.2	18 (64.3)	10 (62.5)	1.08	1.00
	< 3.2	10 (35.7)	6 (37.5)		
CRP (mg/dL)	> 0.5	13 (46.4)	8 (50.0)	0.87	1.00
	≥ 0.5	15 (53.6)	8 (50.0)		
Hemoglobin (g/dL)	≥ 12.0	5 (17.9)	4 (25.0)	0.65	0.70
	< 12.0	23 (82.1)	12 (75.0)		
Baseline BW loss	5–10%	15 (53.6)	11 (68.8)	0.52	0.36
	≥ 10%	13 (46.4)	5 (31.3)		
Tumor type	CRC	10 (35.7)	6 (37.5)		0.20
	GC	10 (35.7)	3 (18.8)		
	PC	8 (28.6)	7 (43.8)		
Disease status	UR-LA	7 (25.0)	3 (18.8)		0.08
	Meta-static	12 (42.9)	8 (50.0)		
	Re-currence	9 (32.1)	5 (31.3)		
No. of previous regimens	0–1	22 (78.6)	11 (68.8)	1.67	0.49
	≥ 2	6 (21.4)	5 (31.3)		
History of gastric surgery	No	22 (78.6)	14 (87.5)	0.52	0.69
	Yes	6 (21.4)	2 (12.5)		

ECOG PS, Eastern Cooperative Oncology Group performance status; CRP, C-reactive protein; BW, body weight; CRC, colorectal cancer; GC, gastric cancer; PC, pancreatic cancer; UR-LA, unresectable locally advanced

**Fig. 4** Evaluation time point of maximum weight gain for each primary tumor site GC: gastric cancer, PC: pancreatic cancer, CRC: colorectal cancer**Table 3** Association of disease control with anamorelin efficacy ($n = 44$)

Disease control	ANAM Responder ($n = 28$)	ANAM Non-responder ($n = 16$)	Odds ratio (95% CI: 1.11–23.20) $p = 0.0238$
Yes, n (%)	21 (75.0)	6 (37.5)	4.80
No, n (%)	7 (25.0)	10 (62.5)	

ANAM, anamorelin; 95% CI, 95% confidence interval

Table 4 Treatment-related adverse events: safety analysis ($n = 74$)

Event	No. (%)	
	All Grades	Grade 3–4
All	40 (54.1)	3 (4.0)
Hyperglycemia	10 (13.5)	2 (2.7)
Fatigue	9 (12.2)	1 (1.3)
Nausea	5 (6.7)	0 (0.0)
Stomach pain	4 (5.3)	0 (0.0)
Diarrhea	3 (4.0)	0 (0.0)
Edema	3 (4.0)	0 (0.0)
Vomiting	2 (2.7)	0 (0.0)
Abnormal ECG	2 (2.7)	0 (0.0)
Hyperhidrosis	1 (1.3)	0 (0.0)
Hypertension	1 (1.3)	0 (0.0)

ECG, electrocardiogram

Table 5 Patient background with hyperglycemia due to anamorelin

No.	Grade of hyperglycemia	Primary site	History of diabetes mellitus	Anamorelin discontinuation within 3 weeks
1	Grade 1	CRC	IGT	
2	Grade 1	GC	none	
3	Grade 2	GC	none	
4	Grade 2	GC	Diabetes Mellitus	
5	Grade 2	PC	Diabetes Mellitus	
6	Grade 2	PC	Diabetes Mellitus	
7	Grade 2	PC	Diabetes Mellitus	yes
8	Grade 3	PC	Diabetes Mellitus	yes
9	Grade 3	PC	IGT	
10	Grade 3	PC	Diabetes Mellitus	

CRC, colorectal cancer; GC, gastric cancer; PC, pancreatic cancer; IGT, impaired glucose tolerance

for improvement in anorexia, the ANAM response rate in this study was 63.6%, consistent with the ANAM response rate observed in the ONO-7643-05 trial. Given the comparable results of these and the ONO-7643-05 studies, body weight rather than lean body mass along with appetite maintenance can be used to determine ANAM's efficacy in clinical practice.

Further, among patients with gastric and pancreatic cancers, the maximum weight gain was observed at 6 weeks, whereas among those with colorectal cancer, it was frequently observed after 9 weeks. This result reflects

the differences in the propensity for disease progression based on the cancer type.

Currently, the predictive factors for the effectiveness of ANAM remain unclear. When evaluating ANAM efficacy and background factors in this study, Fisher's exact test revealed that only age > 75 years was associated with poor ANAM efficacy. Cancer cachexia is a condition that progresses in proportion to the worsening of the underlying disease with systemic inflammation [1], and when there is a significant response to chemotherapy, cachexia can improve, and body weight gain may be achieved with chemotherapy alone. Therefore, we hypothesized that the effectiveness of ANAM could be anticipated in cases where disease control was achieved through chemotherapy. Therefore, we investigated the relationship between control of the underlying disease and the effectiveness of ANAM. The results showed that significantly more patients with disease control experienced ANAM efficacy in terms of the timing of ANAM implementation. While these results are intriguing, it is uncertain whether this weight maintenance and enhancement in appetite were solely achieved through disease control, with or without ANAM. It may be difficult to improve cachexia with chemotherapy alone, and the combination of ANAM with chemotherapy may help improve cachexia.

Hyperglycemia was the most frequent treatment-related AE. In addition to hyperglycemia, most events were of low-grade severity that can be safely managed in clinical practice and have little effect on anticancer therapies. Only in two cases of hyperglycemia and one case of fatigue, the severity was grade 3 or higher. The incidence of hyperglycemia was higher in our study than in the ONO-7643-05 study. Takeda et al. reported that a history of diabetes is a risk factor for hyperglycemia during ANAM treatment for pancreatic cancer [24]. The proportion of patients with pancreatic cancer was higher in our study than in the ONO-7643-05 study (36.5% vs. 10.0%). This may have led to a higher frequency of hyperglycemia in our study which included a large number of patients with pancreatic cancer. Ando et al. [25]. reported that impaired glucose tolerance is a risk factor for ANAM-induced hyperglycemia, which is consistent with our findings. Further research is necessary to ascertain how pancreatic cancer and impaired glucose tolerance interact with ANAM-induced hyperglycemia.

However, whether ANAM should be continued with the addition of insulin or diabetes medications or discontinued when hyperglycemia occurs is unclear. In our study, two of the ten patients with hyperglycemia discontinued ANAM within 3 weeks. However, the ANAM response rate of the patients who were able to continue was 37.5%. Thus, even if hyperglycemia is observed, it may be advantageous to continue ANAM with induction of insulin therapy or an oral hypoglycemic agent.

This study has some limitations. First, this retrospective study was conducted at a single institution and included a small number of patients. Second, because this is a retrospective study, it lacks information on body composition and functional outcome and an assessment of anorexia using a questionnaire. Third, in clinical practice, it is impossible to perform an image assessment at every 3-week evaluation point, and the association between anamorelin efficacy and disease status may not be accurately assessed. The issues raised in our study warrant further investigation by means of large-scale, multicenter studies to determine the patient characteristics that are particularly suitable for ANAM.

Conclusions

In clinical practice, ANAM increases body weight and improves the appetite of patients with cachexia due to advanced gastrointestinal cancer. The efficacy of ANAM was influenced by background factors of older age. In addition, efficacy of ANAM tended to be diminished in patients with progressive disease. Furthermore, most ANAM-related AEs were manageable.

Abbreviations

ANAM	Anamorelin
CTCAE	Common terminology criteria for adverse events
ECOG PS	Eastern cooperative oncology group performance status
BSC	Best supportive care
AE	Adverse event

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Author contributions

ANi and SH designed this study. ANi, SH, and ANo analyzed the patient data. KF, KO, TT, TK, AT, TY, HY, YO, and KY contributed to the data interpretation and drafting of the manuscript. All the authors have read and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All procedures involving human participants were performed according to the ethical standards of the National Research Committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Shizuoka Cancer Center Institutional Review Board (Approval No. J2022-136-2022-1-3).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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