Anti-emetic therapy during first-line chemotherapy containing zolbetuximab for HER2-negative, Claudin 18.2-positive unresectable advanced/recurrent gastric cancer (Flash report of the clinical practice guidelines for antiemesis)

English Version

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1. Introduction

Zolbetuximab (Vyloy®, Astellas Pharma Inc., Tokyo, Japan), an anti-claudin 18.2 antibody, was approved for claudin 18.2-positive unresectable advanced/recurrent gastric cancer (AGC) on March 26, 2024. It has been commercially available in Japan since June 12, 2024. Chemotherapy containing zolbetuximab is expected to improve the clinical outcomes of patients with claudin 18.2-positive (moderate-to-strong [2+/3+] membranous staining in ≥75% of tumor cells by immunohistochemical assay) AGC in clinical practice. The clinical utility and significance of zolbetuximab are reported in a flash report (in Japanese) by the Japanese Gastric Cancer Association (https://www.jgca.jp/wp-content/uploads/2024/05/SPOTLIGHT_GLOW_202405.pdf).

However, as zolbetuximab is highly emetic, anti-emetic therapy should be administered appropriately. Although guidelines are generally made after a systematic review of published evidence, there have been few reports of anti-emetic therapy during zolbetuximab containing chemotherapy. Therefore, this flash report provides information on the use of anti-emetic therapy during chemotherapy containing zolbetuximab to avoid delay in the appropriate use of anti-emetic therapy in clinical practice. This report is based on not only published papers but also reports from medical meetings, review reports by the Ministry of Health, Labour and Welfare, Japan, the guide for the appropriate use of zolbetuximab proposed by the company, and the opinions of the Japanese doctors who participated in the clinical trials SPOTLIGHT and GLOW.

2. Summary of clinical trials

In the phase III trials SPOTLIGHT[1)] and GLOW[2)], zolbetuximab was compared with placebo in combination with mFOLFOX6 (5-fluorouracil/leucovorin + oxaliplatin) and CAPOX (capecitabine + oxaliplatin), respectively, as first-line chemotherapy for HER2-negative, claudin-positive gastric or gastroesophageal junction adenocarcinoma. The findings consistently demonstrated the survival benefits of zolbetuximab.

3. Emetic risk of chemotherapy containing zolbetuximab

Because claudin 18.2 is expressed in the tight junctions of the gastric mucosal epithelium, nausea and vomiting are considered to be caused by the action of zolbetuximab on

normal gastric mucosa. In a phase I trial of zolbetuximab monotherapy, nausea and vomiting were observed. The incidences of nausea and vomiting in the SPOTLIGHT and GLOW trials are presented in Table 1. In both trials, dose reduction of zolbetuximab and placebo owing to nausea or vomiting was not allowed.

Table 1: Incidence of nausea and vomiting in the SPOTLIGHT and GLOW trials[3)]

Adverse Events (MedDRA ver.25.0, preferred term)	SPOTLIGHT trial				GLOW trial			
	Vyloy® + mFOLFOX6 (n=279)		Placebo + mFOLFOX6 (n=278)		Vyloy® + CAPOX (n=254)		Placebo + CAPOX (n=249)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Nausea/ Vomiting*	249 (89.2)	61 (21.9)	188 (67.6)	24 (8.6)	208 (81.9)	42 (16.5)	149 (59.8)	10 (4.0)
Nausea	230 (82.4)	45 (16.1)	169 (60.8)	18 (6.5)	174 (68.5)	22 (8.7)	125 (50.2)	6 (2.4)
Vomiting	188 (67.4)	45 (16.1)	99 (35.6)	16 (5.8)	168 (66.1)	31 (12.2)	77 (30.9)	9 (3.6)
Retching**	6 (2.2)	1 (0.4)	3 (1.1)	0	1 (0.4)	0	0	0

Number of patients (%), *: nausea, vomiting, cyclic vomiting syndrome, vomiting projectile, or retching, according to MedDRA ver. 25.0 preferred term, **: dry heaves

Considering the high incidence of nausea and vomiting reported in the SPOTLIGHT and GLOW trials, regardless of the recommendation of prophylactic use of 5-HT3 and NK1 receptor antagonists for anti-emetic therapy, chemotherapy containing zolbetuximab in combination with fluoropyrimidine and oxaliplatin should be classified as high emetic risk. Notably, the incidence of nausea and vomiting was relatively lower in patients with prior gastrectomy than in those with a preserved stomach. However, nausea and vomiting were often experienced even in patients who have undergone total gastrectomy.

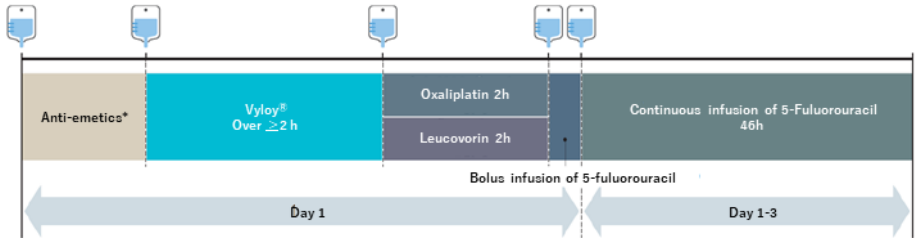
4. Onset time of nausea and vomiting during chemotherapy containing zolbetuximab

Fig. 1 shows the administration schedules of zolbetuximab in combination with mFOLFOX6 and CAPOX; zolbetuximab was administered immediately after the administration of anti-emetic agents. The median time (range) to the occurrence of

nausea was 50 (0–371) and 38 (0–371) min in the SPOTLIGHT and GLOW trials, respectively, and that of vomiting was 55 (0–100) and 59 (0–264) min, respectively, indicating that nausea and vomiting occurred during the infusion of zolbetuximab[4]. These results indicate that prevention and early management of nausea and vomiting are necessary during chemotherapy with zolbetuximab.

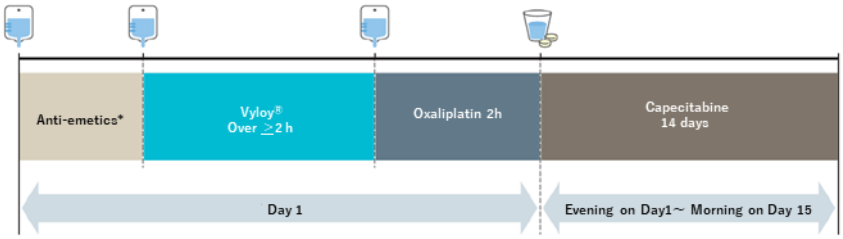
Figure 1: Administration schedule of chemotherapy containing zolbetuximab[3]

a) mFOLFOX6 + zolbetuximab



Intravenous antiemetic premedication was administered before zolbetuximab, and oral antiemetic premedication was given at least 30 minutes prior to zolbetuximab.

b) CAPOX + zolbetuximab



*: antiemetics was administered more than 30 minutes before Vyloy®

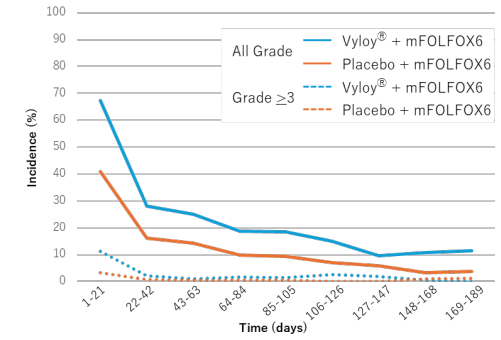
Intravenous antiemetic premedication was administered before zolbetuximab, and oral antiemetic premedication was given at least 30 minutes prior to zolbetuximab.

Anti-emetic therapy is particularly important in the first cycle, in which the incidence of nausea and vomiting was the highest, because the dose of zolbetuximab was higher than that in subsequent cycles, in which the incidence of nausea and vomiting declined (Figure 2). Although no reports have been published regarding the incidence of nausea and vomiting on day 2 or later, the Japanese doctors who participated in the two trials stated that delayed emesis was observed, partly owing to the combination of agents (fluoropyrimidine + oxaliplatin).

Figure 2: Incidence of nausea and vomiting in each period[3)]

a) Nausea

SPOTLIGHT



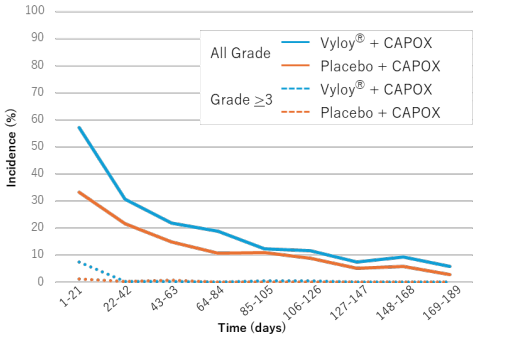
All Grade N (%)

Vyloy® + mFOLFOX	188/279 (67.4)	78/279 (28.0)	66/265 (24.9)	47/252 (18.7)	44/238 (18.5)	34/228 (14.9)	21/220 (9.5)	23/212 (10.8)	22/193 (11.4)
Placebo + mFOLFOX	114/278 (41.0)	45/278 (16.2)	38/268 (14.2)	26/264 (9.8)	24/254 (9.4)	16/233 (6.9)	13/225 (5.8)	7/213 (3.3)	7/186 (3.8)

Grade ≥3 N (%)

Vyloy® + mFOLFOX	31/279 (11.1)	6/279 (2.2)	2/265 (0.8)	4/252 (1.6)	3/238 (1.3)	6/228 (2.6)	4/220 (1.8)	1/212 (0.5)	0/193
Placebo + mFOLFOX	9/278 (3.2)	2/278 (0.7)	1/268 (0.4)	1/264 (0.4)	1/254 (0.4)	0/233	0/225	2/213 (0.9)	2/186 (1.1)

GLOW



All Grade N (%)

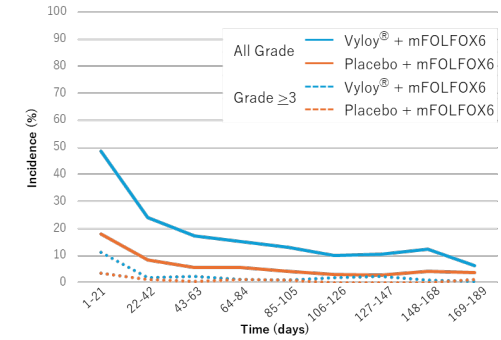
Vyloy® + CAPOX	145/254 (57.1)	78/254 (30.7)	51/233 (21.9)	40/212 (18.9)	25/201 (12.4)	22/188 (11.7)	13/174 (7.5)	14/151 (9.3)	8/133 (6.0)
Placebo + CAPOX	83/249 (33.3)	54/249 (21.7)	35/234 (15.0)	24/222 (10.8)	23/209 (11.0)	17/188 (9.0)	9/176 (5.1)	9/156 (5.8)	4/135 (3.0)

Grade ≥3 N (%)

Vyloy® + CAPOX	19/254 (7.5)	1/254 (0.4)	1/233 (0.4)	0/212	1/201 (0.5)	1/188 (0.5)	0/174	0/151	0/133
Placebo + CAPOX	3/249 (1.2)	1/249 (0.4)	2/234 (0.9)	0/222	0/209	0/188	0/176	0/156	0/135

b) Vomiting

SPOTLIGHT



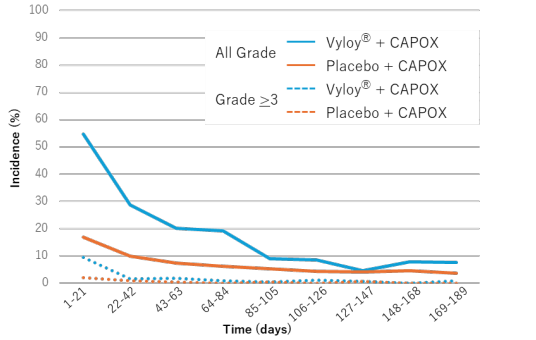
All Grade N (%)

Vyloy® + mFOLFOX	136/279 (48.7)	67/279 (24.0)	46/265 (17.4)	38/252 (15.1)	31/238 (13.0)	23/228 (10.1)	23/220 (10.5)	26/212 (12.3)	12/193 (6.2)
Placebo + mFOLFOX	50/278 (18.0)	23/278 (8.3)	15/268 (5.6)	15/264 (5.7)	11/254 (4.3)	7/233 (3.0)	6/225 (2.7)	9/213 (4.2)	7/186 (3.8)

Grade ≥3 N (%)

Vyloy® + mFOLFOX	31/279 (11.1)	5/279 (1.8)	6/265 (2.3)	3/252 (1.2)	2/238 (0.8)	4/228 (1.8)	5/220 (2.3)	2/212 (0.9)	1/193 (0.5)
Placebo + mFOLFOX	10/278 (3.6)	3/278 (1.1)	1/268 (0.4)	3/264 (1.1)	2/254 (0.8)	0/233	0/225	0/213	2/186 (1.1)

GLOW



All Grade N (%)

Vyloy® + CAPOX	139/254 (54.7)	73/254 (28.7)	47/233 (20.2)	41/212 (19.3)	18/201 (9.0)	16/188 (8.5)	8/174 (4.6)	12/151 (7.9)	10/133 (7.5)
Placebo + CAPOX	42/249 (16.9)	25/249 (10.0)	17/234 (7.3)	14/222 (6.3)	11/209 (5.3)	81/188 (4.3)	7/176 (4.0)	7/156 (4.5)	5/135 (3.7)

Grade ≥3 N (%)

Vyloy® + CAPOX	24/254 (9.4)	4/254 (1.6)	4/233 (1.7)	2/212 (0.9)	1/201 (0.5)	2/188 (1.1)	1/174 (0.6)	0/151	1/133 (0.8)
Placebo + CAPOX	5/249 (2.0)	2/249 (0.8)	1/234 (0.4)	0/222	1/209 (0.5)	0/188	1/176 (0.6)	0/156	0/135

5. Nausea and vomiting associated with the use of anti-emetic therapies

In the SPOTLIGHT and GLOW trials, 5-HT3 and NK1 receptor antagonists were recommended for anti-emetic therapy because combination cytotoxic chemotherapy with mFOLFOX6 and CAPOX is classified as moderate emetic risk. In contrast, no steroid use was recommended or steroid use was kept to a minimum (not prohibited) because of the adverse impact of steroids on the mechanism of zolbetuximab. Nevertheless, steroid was used in approximately half of the patients, resulting in a relatively lower incidence of nausea and vomiting of all grades than in those not receiving a steroid (Tables 2 and 3). In addition, subset analysis showed that the clinical outcomes of patients receiving a steroid were slightly better than those of patients who did not receive steroid. The number of patients who did not receive a 5-HT3 receptor antagonist was too small for inferring its anti-emetic efficacy when used with zolbetuximab. The anti-emetic efficacy of NK1 receptor antagonists was favorable but not consistent. The incidence of grade $\geq$3 nausea and vomiting was lower in the SPOTLIGHT trial, whereas that of all grades was lower in the GLOW trial. However, because combined chemotherapy with fluoropyrimidine and oxaliplatin has a moderate emetic risk, triplet anti-emetic therapy with a steroid and antagonists of the 5-HT3 and NK1 receptors is necessary. No reports have been published on the incidence of nausea and vomiting associated with olanzapine use. Notably, anti-histamine agents were used to prevent infusion reactions in approximately 20% of the patients, and the incidence of nausea and vomiting was relatively low in the GLOW trial.

Table 2: Nausea and vomiting associated with prophylactic use of anti-emetic agent on day 1 of the first infusion of zolbetuximab[3)]

Use of anti-emetic agent		SPOTLIGHT				GLOW			
		n	All Grades	Grade ≥3	Serious	n	All Grades	Grade ≥3	Serious
Any	(+)	269	164 (61.0)	29 (10.8)	10 (3.7)	252	153 (60.7)	18 (7.1)	5 (2.0)
	(-)	7	4 (57.1)	0	0	1	1 (100.0)	1 (100.0)	1 (100.0)
Any of the below	(+)	268	164 (61.2)	29 (10.8)	10 (3.7)	251	152 (60.6)	18 (7.2)	5 (2.0)
	(-)	8	4 (50.0)	0	0	2	2 (100.0)	1 (50.0)	1 (50.0)
NK1 receptor antagonist	(+)	180	108 (60.0)	14 (7.8)	5 (2.8)	142	80 (56.3)	10 (7.0)	5 (3.5)
	(-)	96	60 (62.5)	15 (15.6)	5 (5.2)	111	74 (66.7)	9 (8.1)	1 (0.9)
5-HT3 receptor antagonist	(+)	263	162 (61.6)	29 (11.0)	10 (3.8)	250	152 (60.8)	18 (7.2)	5 (2.0)
	(-)	13	6 (46.2)	0	0	3	2 (66.7)	1 (33.3)	1 (33.3)
Anti-histamine	(+)	51	31 (60.8)	6 (11.8)	1 (2.0)	51	28 (54.9)	3 (5.9)	0
	(-)	225	137 (60.9)	23 (10.2)	9 (4.0)	202	126 (62.4)	16 (7.9)	6 (3.0)
Corticosteroid	(+)	83	44 (53.0)	9 (10.8)	1 (1.2)	84	46 (54.8)	6 (7.1)	0
	(-)	193	124 (64.2)	20 (10.4)	9 (4.7)	169	108 (63.9)	13 (7.7)	6 (3.6)

6. Nausea and vomiting associated with combinations of anti-emetic agents

Although it is difficult to definitively recommend a combination anti-emetic therapy for zolbetuximab-containing chemotherapy owing to the small number of patients who received each combination, a low incidence of nausea and vomiting was observed in patients who received triplet therapy comprising a steroid and antagonists of the 5-HT3 and NK1 receptors, along with other drugs (Table 3). However, detailed information is not available on the drugs denoted as “others”. According to comments from the Japanese doctors who participated in the clinical trials, the patients were often administered anti-histamine agents and/or olanzapine in addition to the triplet anti-emetic therapy, as well as dopamine D2 receptor antagonists such as metoclopramide and domperidone.

Table 3: Incidence of nausea and vomiting associated with prophylactic combination use of anti-emetic agents during the first infusion of zolbetuximab[4)]

Combination of anti-emetic agents				SPOTLIGHT					GLOW				
				n	Nausea		Vomiting		n	Nausea		Vomiting	
5-HT3	Steroid	NK-1	Others		All Grade	Grade ≥3	All Grade	Grade ≥3		All Grade	Grade ≥3	All Grade	Grade ≥3
○				30	16 (53)	4 (13)	15 (50)	5 (17)	38	14 (37)	0	17 (45)	0
○	○			29	13 (45)	3 (10)	10 (34)	4 (14)	20	10 (50)	1 (5)	12 (60)	0
○	○	○		37	19 (51)	2 (5)	13 (35)	2 (5)	25	10 (40)	1 (4)	7 (28)	3 (12)
○	○	○	○	30	14 (47)	0	9 (30)	1 (3)	25	7 (28)	1 (4)	7 (28)	1 (4)
○	○		○	25	12 (48)	2 (8)	12 (48)	3 (12)	15	7 (47)	1 (7)	7 (47)	1 (7)
○		○		69	39 (57)	4 (6)	25 (36)	4 (6)	68	33 (49)	0	31 (46)	6 (9)
○		○	○	43	22 (51)	4 (9)	15 (35)	2 (5)	25	10 (40)	2 (8)	9 (36)	3 (12)

Number of patients (%), 5HT-3: serotonin receptor antagonist, NK-1: neruokinin-1 receptor antagonist

7. Association between emesis and the infusion rate of zolbetuximab

Emesis associated with zolbetuximab has been reported to depend on infusion rate. In patients who required infusion modification owing to adverse events, the initial infusion rates were higher than those in patients who did not require infusion modification (Table 4). Nausea and vomiting were the most frequent reasons for infusion modification.

Table 4: Infusion modifications required because of adverse events (AEs), either infusion-related reactions (IRR) or non-IRR, during the first zolbetuximab infusion[4)]

		SPOTLIGHT		GLOW	
Infusion modification required because of any AE		**Yes**	**No**	**Yes**	**No**
No. of patients		96	183	52	202
No. (%) of patients experiencing nausea/vomiting		82 (85)	90 (49)	41 (79)	116 (57)
No. of patients with available infusion rate data		64	178	43	198
Initial infusion rate (mL/h)	**Mean**	221	167	194	126
	Median	176	100	147	90

The Japanese package insert recommends that zolbetuximab be administered over 2 h or more and that the infusion rate can be increased accordingly when the feasibility of the patient is good 30–60 min after treatment initiation (Table 5).

Table 5: Infusion rate of zolbetuximab recommended in the Japanese package insert[5)]

Dose	Infusion Rate	
	From start of infusion to 30-60 minutes	Subsequent Infusion Rate
800 mg/m^2	100 mg/m^2/h	200–400 mg/m^2/h
600 mg/m^2	75 mg/m^2/h	150–300 mg/m^2/h
400 mg/m^2	50 mg/m^2/h	100–200 mg/m^2/h

However, the infusion rate after 30–60 min (Table 6) showed wide variation. In both the SPOTLIGHT and GLOW trials, a step-by-step increase in infusion rate was recommended. For example, as the final concentration of zolbetuximab was set at 2.0 mg/mL and the infusion volume was 800 mL (1600 mg) in a patient with body surface area (BSA) of 2.0 m^2, the infusion rate was increased by three or more steps: 100 mL/h during the initial 30 min ⇒ 200 mL/h during the subsequent 30–60 min ⇒300–400 mL/h thereafter ⇒ higher rate if the feasibility of the patients was confirmed. Furthermore, since nausea and vomiting improved after interruption and/or reduction of infusion rate, interruption and/or adjustment of infusion rate should be considered upon occurrence of nausea and vomiting. The Japanese package insert of zolbetuximab recommends "infusion of zolbetuximab is interrupted when grade $\geq$2 nausea/vomiting appears until recovery to grade $\leq$1, and then it can be restarted at the reduced infusion rate". In contrast, the infusion rate can be increased at the second or later administration of zolbetuximab in patients whose nausea or vomiting is mild or not observed at the first administration.

8. Proposal from the Working group

After the introduction of zolbetuximab in clinical practice, optimal anti-emetic therapy should be administered to maintain the quality of life of the patient and to continue the treatment, considering the following issues.

- Emesis is an on-target adverse event of zolbetuximab.
- Chemotherapy containing zolbetuximab in combination with fluoropyrimidine and oxaliplatin is classified as high emetic risk.
- Primary prevention and early management of nausea and vomiting are necessary because they occur within 1 h after initiation of zolbetuximab infusion, especially in the first cycle where the zolbetuximab dose is the highest. Although the incidences of nausea and vomiting decrease in the second or later cycles, continuing the anti-emetic therapy appropriately is important.
- Because the combination chemotherapy, fluoropyrimidine + oxaliplatin, has moderate emetic risk, triplet anti-emetic therapy comprising a steroid and 5-HT3 and NK1 receptor antagonists is essential for primary prevention of nausea and vomiting. While the treatments indicated as “triplet + others” showed the most favorable anti-emetic effects in the clinical trials, the drugs denoted as “others”, such as anti-histamine agents or olanzapine, were not unified.
- However, the anti-emetic effect of anti-histamine agents for chemotherapy-induced emesis has not been confirmed in the clinical trials; the drowsiness induced by anti-histamine agents is speculated to be associated with reduced emesis, as per the opinions of the Japanese doctors who participated in the clinical trials.
- Because of the early onset of zolbetuximab-induced nausea or vomiting, the usual administration of olanzapine in the evening after chemotherapy cannot prevent emesis. Olanzapine administration can be considered in the morning on the day of chemotherapy or the night before chemotherapy. Dopamine receptor antagonists and/or rescue drugs should be added at appropriate time points.
- Because more than half the patients experienced nausea or vomiting with any anti-emetic therapy in the clinical trials, other anti-emetic management strategies are required. Because emesis related to zolbetuximab depended on its infusion rate and it was improved by interruption or reduction of infusion rate, careful adjustment of the infusion rate is important: 1) start at a low rate, 2) increase gradually, 3) interrupt or reduce the infusion rate immediately after occurrence of emesis, 4) find the optimal infusion rate for each patient. Hospitalization can be proposed,

especially for the first cycle, which may require a long infusion time following rate adjustment.

- Although no data has been reported on delayed emesis, the Japanese doctors who participated in the clinical trials state that some patients experienced it. The use of olanzapine, which the guideline recommends for chemotherapies with high emetic risk, is preferred to prevent delayed emesis.
- Dose reduction of zolbetuximab because of nausea or vomiting should be considered carefully because it was not allowed in the clinical trials.
- Chemotherapy with zolbetuximab should be started after the multi-disciplinary team provides adequate information including self-management for emesis at home to enable each patient to receive treatment without worries.
- Because information on chemotherapy with zolbetuximab is limited to clinical trials, the adverse events and efficacy in each patient needs to be observed carefully and managed appropriately in clinical practice.

References

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3) Guide for optimal use of zolbetuximab (in Japanese)

4) Shitara K, Pophale R, Matney C, Matsangou M, Park JW, Oh M, Bhattacharya P, Ranganath R. Management of nausea and vomiting following first-line zolbetuximab + chemotherapy treatment in CLDN18.2+, HER2–, locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma: analysis from the phase 3 SPOTLIGHT and GLOW studies. Abst No.372, ASCO-GI, 2024

5) Japanese package insert of zolbetuximab

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