Zolbetuximab – Real-world Evidence on Incidence and Management of Nausea and Vomiting

- Three single-institute observational studies evaluated various protocols for managing zolbetuximab-induced nausea and vomiting in patients with advanced gastric cancer.[1–3]
    - Antiemetic and premedication protocols were administered across all three studies and included medication such as: 5-HT_3 receptor blockers, NK-1 receptor blockers, dexamethasone (oral and IV), H_1 blockers, H_2 blockers. Optional premedication included olanzapine, alprazolam or lorazepam.
- Please note that the studies summarized below were conducted in Japan, and adhered to local prescribing information.
- This real-world evidence is provided for educational purposes only. This document may not contain all the information needed to use this product safely and effectively. Please be sure to review the full prescribing information for this product.

Real-world data

Shimozaki et al. 2025[1]

A single-institute registry study evaluated the feasibility and utility of a simplified dosing method and protocol for zolbetuximab-induced gastrointestinal toxicity in 21 patients with advanced gastric cancer.

The protocol was based on the center's experience managing patients in Phase 3 trials and included:

- Administration of antiemetics and premedication for three to five days including:
    - Day 1: 5-HT_3 receptor blocker (palonosetron hydrochloride 0.75 mg), NK-1 receptor blocker (fosnetupitant 235 mg), dexamethasone (9.9 mg) administered via IV, plus H_1 blocker (polaramine 5 mg), H_2 blocker (famotidine 20 mg).
    - Days 2 and 3: oral dexamethasone (4 mg).
    - Days 1 to 5: optional olanzapine (5 mg).
- A simplified dose escalation protocol including a two-stage fixed infusion rate regardless of patients' BSA for the loading dose.
    - The loading dose of zolbetuximab (800 mg/m^2) was administered via IV at 75 mL/h for the first 60 min, then increased to 250 mL/h until fully infused.
    - The infusions of zolbetuximab were diluted with sterile 0.9% sodium chloride to a final concentration of 2 mg/mL in accordance with local prescribing information.
    - If intolerable nausea or vomiting occurred, zolbetuximab administration was withheld for 30 minutes to allow for the administration of additional antiemetic agents, and restarted at a reduced rate after symptoms improved.

In Cycle 1:

- All-grade nausea and vomiting occurred in 81% and 19% of patients, respectively.
- None of the patients experienced nausea and vomiting during the initial 60 minutes when the infusion rate was 75 mL/h.
- Thirteen patients (62%) experienced intolerable nausea with an infusion rate of 250 mL/h, leading to dose interruptions; however, all patients successfully completed zolbetuximab administration.
- Median (range) total infusion time was 257 (154 – 343) minutes.

In Cycle 2, zolbetuximab infusion was well tolerated with a 21% nausea rate and no vomiting.

Narita et al. 2025[2]

A single-institute, observational study evaluated the safety and effectiveness of a protocol for zolbetuximab-induced gastrointestinal toxicity and hypoalbuminemia in 24 patients treated with zolbetuximab as part of standard of care for advanced gastric/gastroesophageal junction cancer.

- Administration of antiemetics and premedication for six days including:[4]
  - Days -1 to 5: oral vonoprazan and rebamipide.
  - Day 1: NK-1 receptor blocker (fosnetupitant), 5-HT_3 receptor blocker (granisetron), dexamethasone (9.9 mg), chlorpheniramine via IV. Acetaminophen and prochlorperazine ± hydroxyzine were used as rescue medication, via IV if needed.
  - Days 2 to 4: oral dexamethasone (4 mg).
  - Days -1 to 4: optional oral olanzapine (5 mg).
- A stepwise infusion rate escalation protocol for Cycle 1:
  - Zolbetuximab was administered via IV infusion on Day 1 of each chemotherapy cycle. The loading dose was 800 mg/m^2, and subsequent doses were 600 or 400 mg/m^2 (for 3-week or 2-week cycles, respectively).
  - Infusions began at 100 mg/m^2/h, and gradually increased if no moderate or severe symptoms arose, at predefined intervals, until the full dose was delivered.
  - The infusions of zolbetuximab were diluted with sterile 0.9% sodium chloride to a final concentration of 2 mg/mL in accordance with local prescribing information.
- Infusion interruptions and immediate bedside availability of rescue medications.

In Cycle 1:

- All-grade acute infusion-related nausea and vomiting occurred in 13 (54%) and six (25%) patients, respectively, and most cases were Grade 1.
- Nine (38%) patients did not experience any infusion-related adverse events.
- No acute Grade ≥ 2 vomiting occurred after implementation of a protocol amendment for rescue medication administration at bedside.
- Six (25%) patients experienced at least one interruption during infusion.
- Median (range) total infusion time was 215 (197 – 332) minutes.

In Cycle 2 and beyond, all-grade acute infusion-related nausea and vomiting occurred in six (23%) patients and one (3%) patient, respectively.[4]

Yakuwa et al. 2025[3]

A single-institute observational study evaluated the safety and feasibility of an outpatient administration protocol for zolbetuximab in five patients with advanced gastric cancer.

- A premedication and antiemetic protocol including:
  - Day -1: oral diphenhydramine hydrochloride and olanzapine (excluding patients with diabetes).
  - Day 1: oral diphenhydramine hydrochloride and olanzapine (excluding patients with diabetes) plus IV dexamethasone, palonosetron, and fosnetupitant. Metoclopramide was used as rescue medication, via IV if needed.
  - Days 2 and 3: optional oral dexamethasone (excluding patients with diabetes).
  - Days -1 to 14: optional alprazolam or lorazepam (in patients with severe anxiety).
  - All Days: oral metoclopramide or alprazolam as rescue medication.
- A hospital-pharmacy collaboration system.
- An administration protocol including infusion rate escalation guidance, as well as monitoring and response protocols for nausea and vomiting.

At data cutoff (November 2024):

- Nausea and vomiting occurred in 60% and 20% of patients, respectively; all cases were Grade 1.
- No Grade ≥ 3 adverse events reported.
- Qualitative analysis of patient experiences revealed minimal nausea compared to expectations, less need for antiemetics than anticipated, and better tolerability than expected.

Abbreviations

5-HT$_3$: serotonin 3 receptor blocker; **BSA**: body surface area; **H$_1$**: histamine type 1; **H$_2$**: histamine type 2; **IV**: intravenous; **NK-1**: neurokinin-1 receptor blocker.

References:

1. Shimozaki K, Ooki A, Yamahata Y, et al. Managing zolbetuximab-induced nausea and vomiting: a proposal for a pragmatic approach in clinical practice. *ESMO Gastrointest. Oncol.* 2025;7:100128. Available at: https://doi.org/10.1016/j.esmogo.2024.100128.

2. Narita Y, Mizuno T, Suda T, et al. Practical Management of Zolbetuximab Administration: The Project VYLOY Initiative. *Cancers*. 2025;17(12):1996. Available at: https://doi.org/10.3390/cancers17121996.

3. Yakuwa E, Shoji Y, Oizumi T, et al. Safety and Feasibility of Outpatient Zolbetuximab Administration in Community Cancer Care: A Mixed-methods Analysis. *Vivo*. 2025;39(2):951-960. Available at: https://doi.org/10.21873/invivo.13900.

4. Narita Y, Mizuno T, Suda T, et al. Supplement to: Practical Management of Zolbetuximab Administration: The Project VYLOY Initiative. 2025;17(12):1996. Available at: https://doi.org/10.3390/cancers17121996.