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ORIGINAL ARTICLE

Consensus guidance for prevention and management of nausea and vomiting in patients treated with zolbetuximab + chemotherapy: a RAND/UCLA modified Delphi panel study

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Background: This study aims to develop consensus-based guidelines to prevent and manage nausea and vomiting in patients treated with zolbetuximab plus chemotherapy.

Materials and methods: An international Delphi panel included 15 experts who were involved in phase II or III clinical studies of zolbetuximab. A rating survey was developed, informed by literature and clinical experience, consisting of hypothetical scenarios of patients and interventions to prevent and manage nausea and vomiting during treatment with zolbetuximab plus chemotherapy. In April 2024, panelists rated the appropriateness of interventions on a scale of 1-9, discussed areas of disagreement in a virtual meeting, and repeated ratings following the meeting. The consensus was summarized based on responses to the second-round survey.

Results: Areas of agreement were broader in the second-round survey than in the first-round survey, with panelists agreeing on 84.8% of ratings (second round) compared with 55.9% (first round). Agreement was reached on at least one management strategy for before and during the first zolbetuximab infusion and subsequent infusions. The Delphi panel endorses using the National Comprehensive Cancer Network® (NCCN®)-recommended regimens for high emetic risk prophylactically. During infusions, the Delphi panel suggested modifying the zolbetuximab infusion rate, interrupting zolbetuximab infusions temporarily for 30-60 min, administering antiemetic medications not used for prophylaxis, and/or providing intravenous hydration.

Conclusions: These consensus-based guidelines can be utilized by clinicians to guide the prevention and management of nausea and vomiting in patients treated with zolbetuximab plus chemotherapy so that patients can continue receiving treatment and achieve benefits.

Key words: stomach cancer, nausea, vomiting, zolbetuximab, claudin 18.2

INTRODUCTION

Gastric and gastroesophageal junction (G/GEJ) cancers are leading causes of cancer deaths worldwide.[1,2] Zolbetuximab is a first-in-class immunoglobulin G1 monoclonal antibody that targets claudin 18 isoform 2 (CLDN18.2), a tight junction protein expressed exclusively in gastric mucosa cells in normal tissue that is retained in G/GEJ adenocarcinomas.[3-6] In the phase III SPOTLIGHT (NCT03504397) and GLOW (NCT03653507) trials, first-line zolbetuximab plus chemotherapy significantly improved progression-free and overall survival in patients with human epidermal growth factor receptor 2 (HER2)-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma whose tumors were CLDN18.2-positive.[7,8] CLDN18.2 positivity was defined as ≥75% of tumor cells demonstrating moderate-to-strong membranous CLDN18 staining using the

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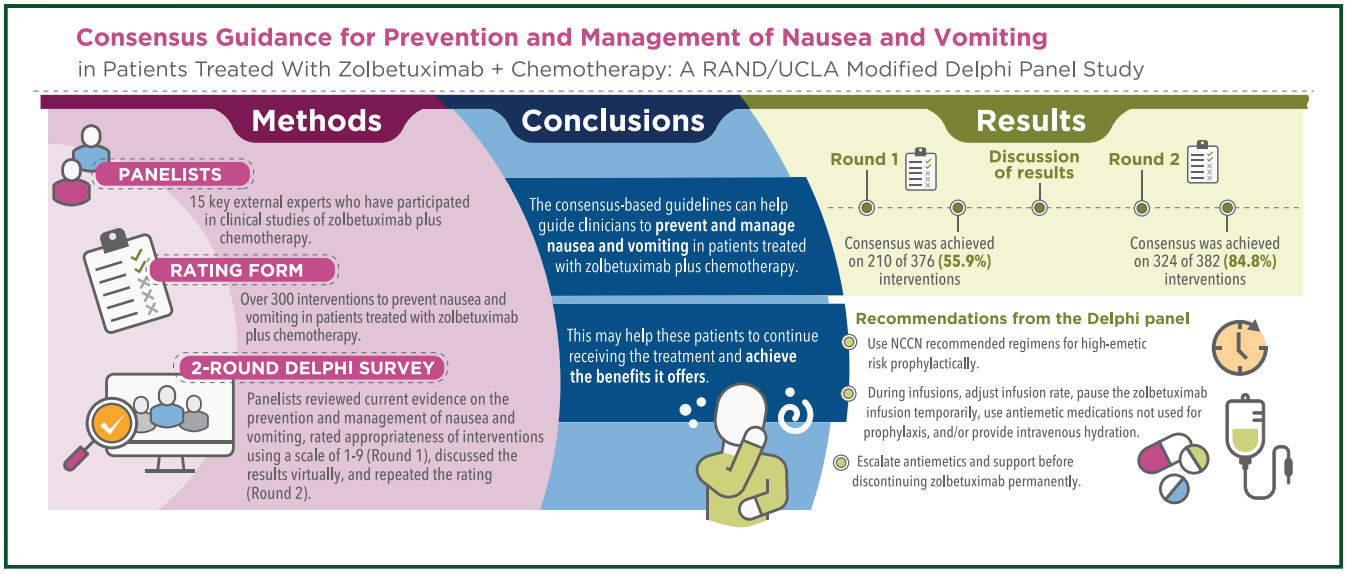
GRAPHICAL ABSTRACT



VENTANA CLDN18 (43-14A) RxDx Assay (**Roche Diagnostics Solutions, Tucson, AZ, USA**).[7,8]

Nausea and vomiting were the most common treatment-emergent adverse events (AEs) with zolbetuximab across all the phase I-III clinical studies.[5-11] In SPOTLIGHT and GLOW, approximately three-quarters of patients experienced nausea and two-thirds of patients experienced vomiting.[7,8] The occurrences of nausea or vomiting were most common during the first zolbetuximab infusion and decreased with subsequent infusions.[7,8] The median time to the first occurrence of nausea and/or vomiting was $<$1 h after starting the first zolbetuximab infusion.[12] Nausea and vomiting led to higher rates of discontinuations in the zolbetuximab arms than in the placebo arms in both SPOTLIGHT and GLOW.[7,8] Overall, patients receiving zolbetuximab plus chemotherapy or placebo plus chemotherapy had similar changes from baseline in patient-reported global health status/quality-of-life scores[13,14]; however, there was a difference in measures of nausea and vomiting between treatment arms that favored the placebo arm over 49 weeks.[14] In the zolbetuximab arms, patient-reported outcome scores for nausea and vomiting worsened during the first few cycles of zolbetuximab treatment and returned to baseline after the first 18-24 weeks without clinically meaningful deterioration.[14]

First-line therapy is important for patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma because many patients may not receive second-line therapy. In SPOTLIGHT and GLOW, ~40%-50% of patients did not receive subsequent anticancer therapies.[7,8] Nausea and vomiting are among the most feared and distressing AEs in patients undergoing chemotherapy.[15] Therefore, preventing and managing these AEs, especially early in the treatment course, is crucial and can improve quality of life and adherence to therapy for patients treated with zolbetuximab plus chemotherapy. However, guidance for the prevention and management of these AEs based on clinical studies of zolbetuximab is limited.

The aim of this study was to reach a global expert consensus on strategies to prevent and manage nausea and vomiting in patients treated with zolbetuximab plus chemotherapy.

MATERIALS AND METHODS

Study design

The RAND/University of California, Los Angeles (UCLA) modified Delphi panel technique is a structured process that was used to facilitate systematic and quantitative evaluation of expert opinion.[16,17] In brief, the study was conducted in steps, including identifying panelists, conducting a targeted literature review, developing a detailed rating form with panelists, asking panelists to complete the first-round survey (round 1), discussing areas of disagreement during a virtual panel meeting, asking panelists to complete the second-round survey (round 2), and summarizing consensus (Figure 1). To ensure impartiality in the findings, a nonaffiliated entity conducted the study. The study did not involve human participants, as defined by 45 Code of Federal Regulations part 46; therefore, it was not subject to institutional review board approval.

Participants and survey design

A group of 15 experts in G/GEJ cancers with experience in managing patients treated with zolbetuximab plus chemotherapy in clinical trials were identified and invited to join the panel. To provide panelists with current evidence on the prevention and management of nausea and vomiting, a targeted literature review was conducted, and an evidence summary was distributed to panelists. The review included all clinical trials of zolbetuximab and guidelines on the prevention and management of nausea and vomiting from NCCN, the American Society of Clinical Oncology (ASCO), and the European Society for Medical Oncology (ESMO).

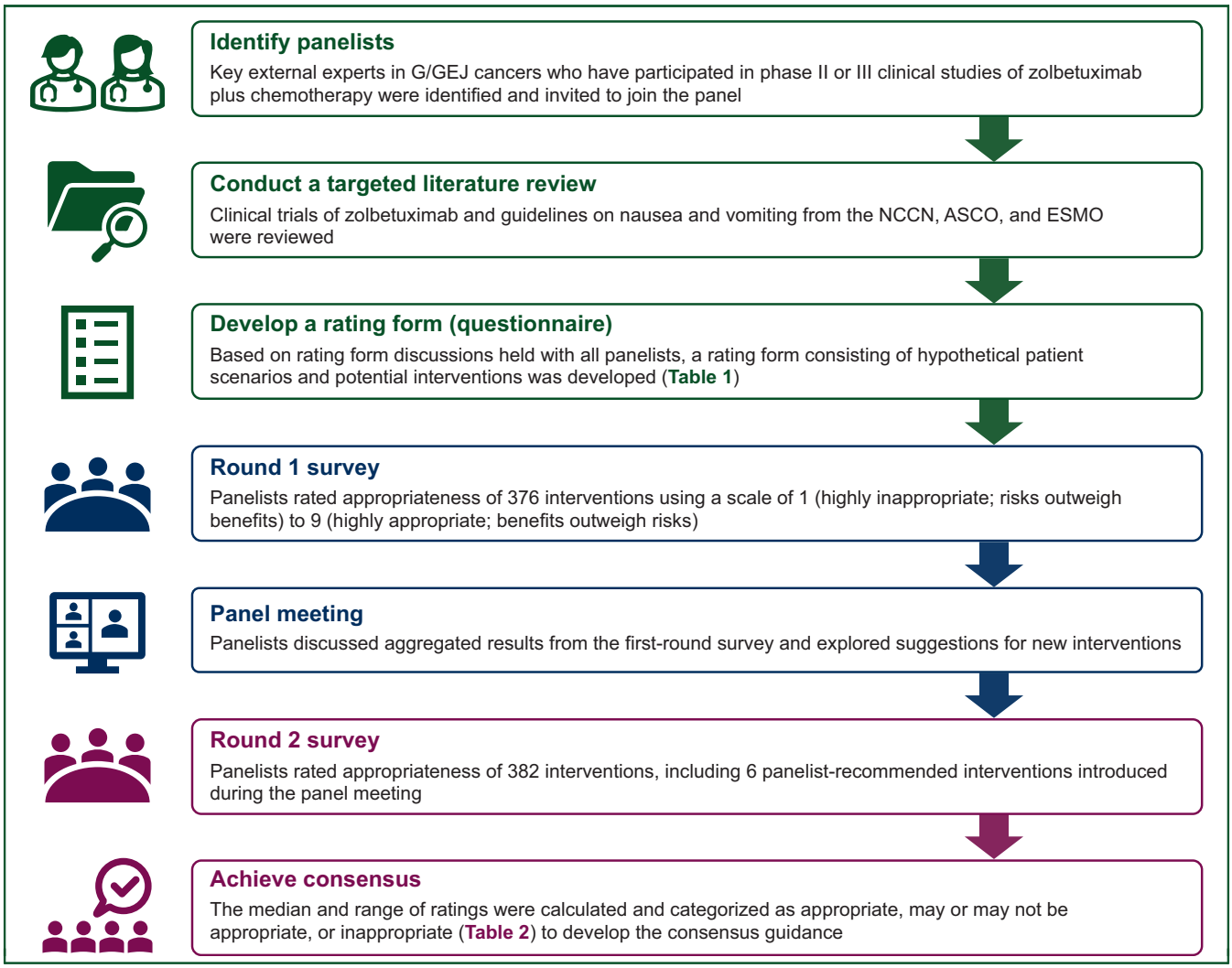


Figure 1. Study design schematic.
ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; G/GEJ, gastric and gastroesophageal junction; NCCN, National Comprehensive Cancer Network.

Next, participating panelists discussed and helped to draft a rating form survey via individual 60-min phone or video calls. During these conversations, panelists were asked open-ended questions to elicit perspectives, expertise, and experiences. Based on discussions with all panelists, a rating form consisting of hypothetical patient scenarios and potential interventions to prevent and manage nausea and vomiting when treating patients with zolbetuximab plus chemotherapy was developed. The rating form included scenarios that described prophylaxis before the first zolbetuximab infusion, plans for subsequent infusions, management during infusions, and additional guidance. An example scenario is presented in Supplementary Table S1, available at https://doi.org/10.1016/j.esmogo.2024.100131.

Survey technique and data analysis

All panelists completed anonymized, individual ratings of appropriateness of interventions using a scale of 1-9, with 1 being 'highly inappropriate; risks outweigh benefits', 5 being 'not sure; risks and benefits seem balanced', and 9 being 'highly appropriate; benefits outweigh risks'. Surveys with missing data were returned to panelists to complete before data analysis. Median and range of ratings were calculated, and disagreement was defined as three or more ratings of 1-3 and three or more ratings of 7-9 within the same scenario (Table 1). For items for which there was agreement, recommendations were categorized into appropriate, uncertain, or inappropriate.

In round 1 (1 April 2024), panelists rated the appropriateness of 376 interventions. Aggregated results from round 1 were distributed to panelists before the panel meeting. In April 2024, a professionally moderated video-based live meeting

Table 1. Analysis of rating scores for the modified Delphi panel

Agreement or disagreement	Median scores	Appropriateness of the intervention
Agreement	7-9	Appropriate
	4-6	Uncertain (may or may not be appropriate)
	1-3	Inappropriate
Disagreement	≥3 ratings of 1-3, and ≥3 ratings of 7-9	Panelists disagreed on the appropriateness of the intervention

was held to discuss the results of round 1, emphasizing areas of disagreement. Augmentations to interventions suggested via the round 1 survey or during the panel discussion were also explored. Following the panel meeting, panelists rated the appropriateness of 382 interventions in round 2 (19 April 2024), including six panelist-recommended items introduced during the panel discussion to specify details of agreed-upon interventions. Results of the round 2 survey were analyzed, and they served as the foundations for the consensus guidance. Additional recommendations for the initiation of a proton pump inhibitor or a histamine-2 receptor blocker, and the application of a scopolamine patch, were incorporated after the round 2 survey, with approval from all panelists.

In addition to the two-round Delphi survey, panelists completed a brief questionnaire about their demographic information and clinical backgrounds. All surveys and questionnaires were circulated electronically.

RESULTS

Demographic data

A group of 15 panelists from the United States, Japan, South Korea, Italy, and Spain participated in the panel. The panel included 13 medical oncologists, 1 oncology nurse practitioner, and 1 oncology pharmacist for a comprehensive clinical perspective. The median duration of practice was 20 years (range 9-34 years). Demographic characteristics and clinical experience of panelists are shown in Table 2.

Results overview

In round 1, panelists reviewed 376 interventions, reaching consensus in 210 interventions (55.9%). During the panel meeting, 6 panelist-recommended interventions were introduced, resulting in a new total of 382 interventions. Following the panel meeting, in round 2, panelists reached consensus in 324 of 382 interventions (84.8%). The consensus-based algorithm is presented in Figure 2, and a plain-language summary is presented in Supplementary Figure S1, available at https://doi.org/10.1016/j.esmogo.2024.100131.

Table 2. Panelists' demographic characteristics and clinical experience

	N = 15, *n* (%)
Sex	
Male	11 (73.3)
Female	4 (26.7)
Race	
White	9 (60.0)
Asian	6 (40.0)
Region	
USA	10 (66.7)
Asia[a]	3 (20.0)
Europe[b]	2 (13.3)
Practice setting	
Academic	14 (93.3)
Nonacademic	1 (6.7)
Time in practice, years	
5-10	3 (20.0)
11-20	5 (33.3)
21-30	6 (40.0)
>30	1 (6.7)
Median (min-max)	20 (9-34)
Patients treated with zolbetuximab in clinical trials, *n*	
0-10	11 (73.3)
11-20	2 (13.3)
21-30	1 (6.7)
>30	1 (6.7)
Median (min-max)	5 (0-60)

[a]Two panelists were from Japan, and one panelist was from South Korea.
[b]One panelist each was from Spain and Italy.

In brief, for prophylaxis, the Delphi panel endorsed NCCN-recommended treatment options for high-emetic-risk parenteral agents for all patients.[18] The Delphi panel discussed NCCN treatment recommendations for regimens with low, moderate, and high emetic risk and noted overlap of different guidelines and the high-emetic-risk regimen. Within the three options of the NCCN-recommended treatments for parenteral high-emetic-risk regimens, the median ratings were as follows: 9.0 for neurokinin-1 (NK-1) antagonist + 5-hydroxytryptamine 3 (5-HT3) receptor antagonist + dexamethasone + olanzapine, 8.0 for NK-1 antagonist + 5-HT3 receptor antagonist + dexamethasone, and 7.0 for 5-HT3 receptor antagonist + dexamethasone+ olanzapine.

For interventions during infusions, panelists discussed modifications of zolbetuximab infusion rate for patients with nausea only, with nausea and one episode of vomiting, or with repeated vomiting. Overall, panelists strongly agreed that zolbetuximab should not be discontinued permanently without first attempting to modify or temporarily interrupt the infusion and/or without providing additional treatment for nausea and vomiting in the absence of hypersensitivity reactions or infusion-related reactions. For patients with any symptoms of nausea or vomiting, panelists agreed that permanently discontinuing zolbetuximab was inappropriate during any of the zolbetuximab infusions, with median ratings of 1.0-3.0. Depending on patient symptoms of nausea and/or vomiting, zolbetuximab infusions may be interrupted temporarily for 30-60 min and restarted at a slower rate or at the rate used before stopping the infusion.

To supplement interventions during infusions, panelists also discussed the appropriateness of intravenous (i.v.) hydration and administering antiemetic medications not used for prophylaxis. During any of the zolbetuximab infusions, the panel agreed that i.v. hydration was appropriate for patients with repeated vomiting (median ratings of 8.0-9.0). They also agreed that the use of antiemetic medications not used for prophylaxis was appropriate in patients with nausea and one episode of vomiting or in patients with repeated vomiting (median ratings of 8.0-9.0).

Panelists also strongly recommended educating patients and clinic staff on what to expect, all giving ratings of 9.0. It should be noted that, although patients treated with zolbetuximab plus chemotherapy may develop nausea and vomiting that are worse than in those treated with chemotherapy only, these symptoms will likely improve after the first infusion and with subsequent infusions.

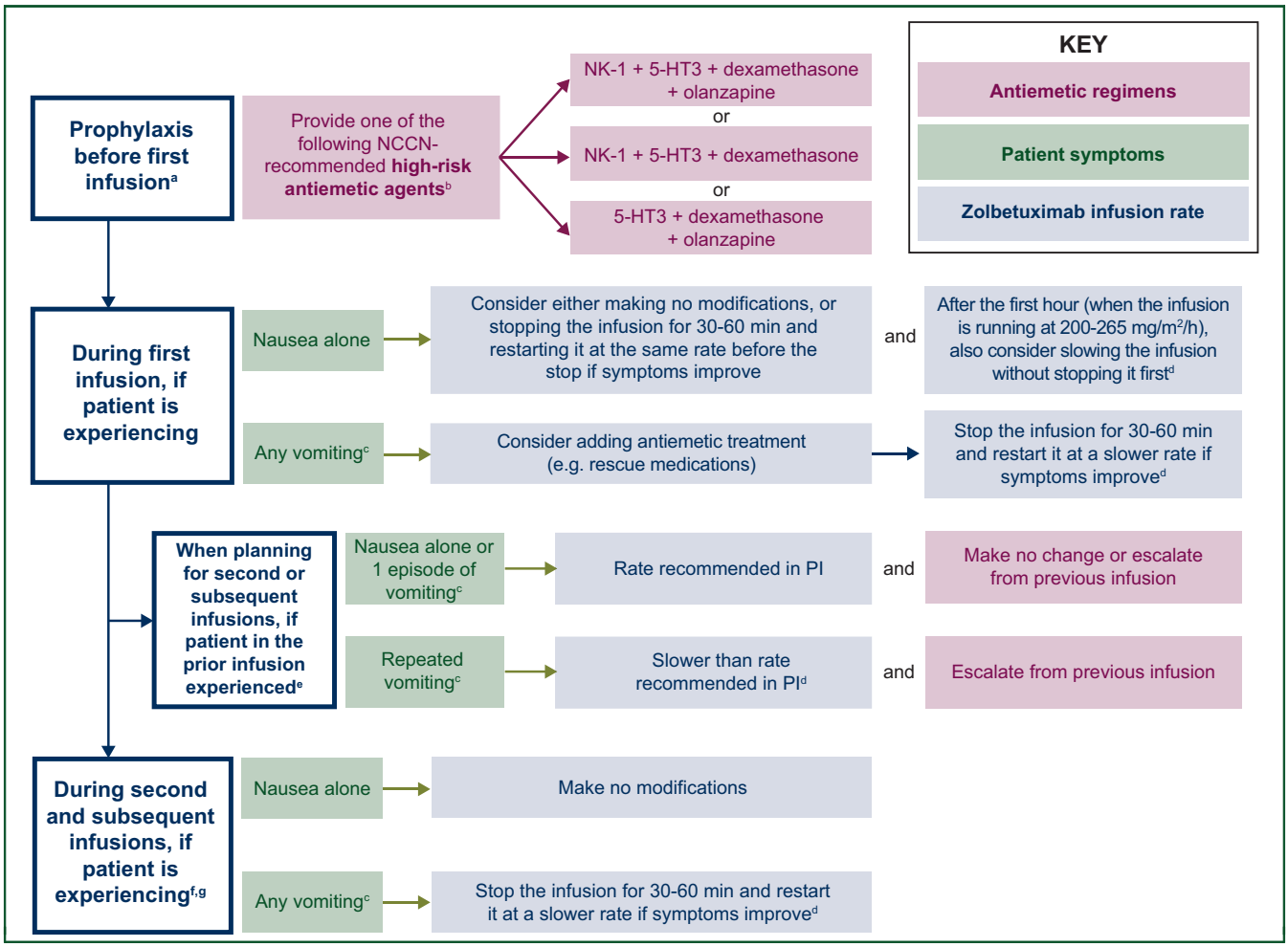


Figure 2. Consensus guidance and essential strategies on the prevention and management of nausea and vomiting in patients treated with zolbetuximab plus chemotherapy.

5-HT3, 5-hydroxytryptamine 3; H2, histamine-2; i.v., intravenous; NCCN, National Comprehensive Cancer Network; NK-1, neurokinin-1; PI, prescribing information; p.o., per oral.

[a]In patients with an intact stomach, consider using an H2 blocker or proton pump inhibitor to prevent dyspepsia, which can mimic nausea. Provide these a few days to 1 week before zolbetuximab treatment for maximal mucosal protection.

[b]NCCN-recommended high-emetic-risk regimens: NK-1 antagonist + 5-HT3 antagonist + dexamethasone + olanzapine, NK-1 antagonist + 5-HT3 antagonist + dexamethasone, or 5-HT3 antagonist + dexamethasone + olanzapine. Either p.o. or i.v. antiemetics may be appropriate based on individual patient's circumstances.

[c]I.v. hydration may be appropriate depending on the individual patient's circumstances.

[d]If infusion was running at PI rate, slow rate by 50%; if infusion had already been slowed to 50%, slow rate by an additional 50% (i.e. 25% of initial rate).

[e]Adjust your plan for subsequent infusions based on the patient's symptoms during prior infusions.

[f]Begin second and subsequent infusions at the rate that was best tolerated during previous infusions (e.g. if the prior infusion was tolerated at the PI rate, subsequent infusions should be given at the same rate; if infusion rate was slowed to 50% of the PI rate and symptoms improved, start subsequent infusions at this rate).

[g]With second and/or subsequent infusions, the degree of nausea and vomiting is expected to diminish. In these cases, patients may tolerate titration of the infusion rate by increments of 25% (e.g. if infusion rate was slowed to 50% and the patient remained asymptomatic for 30-60 min, consider increasing to 75%) back to 100% or to the maximum tolerated dose. Continue to monitor the patient closely for any recurrent symptoms and administer additional antiemetic medications as needed to manage symptoms effectively.

Consensus statements

Prophylaxis before first zolbetuximab infusion. The Delphi panel endorses use of any NCCN-recommended treatment options for high-emetic-risk regimens (Table 3). Given the known risk of nausea and vomiting with zolbetuximab, we recommend against use of NCCN-recommended treatment options for low- and medium-emetic-risk regimens.

In patients with an intact stomach, consider initiating a proton pump inhibitor or a histamine-2 receptor blocker a few days to a week before zolbetuximab for maximal mucosal protection, if the patient is not already taking one.[6]

Management during zolbetuximab infusions. In patients with any vomiting, stop the zolbetuximab infusion for 30-60 min and, if symptoms improve, restart it at a slower rate (i.e. 50% of the rate at the time the infusion was paused).

Begin second or subsequent infusions at the rate that was best tolerated during previous infusions [e.g. if the prior infusion was tolerated at the rate recommended in the prescribing information (PI),[19] second or subsequent infusions should be given at the same rate; if the infusion rate was slowed to 50% of the PI rate and symptoms improved, start second or subsequent infusions at the slowed rate].

Table 3. Prophylaxis before first zolbetuximab infusion
Provide any of the NCCN-recommended treatment options for high-emetic-risk regimens[a]
NK-1 antagonist + 5-HT3 antagonist + dexamethasone + olanzapine[b]
NK-1 antagonist + 5-HT3 antagonist + dexamethasone
5-HT3 antagonist + dexamethasone + olanzapine

5-HT3, 5-hydroxytryptamine 3; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network; NK-1, neurokinin-1.

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[b]Same as the high-emetic-risk regimen recommended by ESMO/MASCC and ASCO.

With second or subsequent infusions, the degree of nausea and vomiting is expected to diminish, as was observed in the phase III trials of zolbetuximab.[7,8] In these cases, patients may tolerate titration of the zolbetuximab infusion rate by increments of 25% (e.g. if the infusion rate was slowed to 50% and the patient remained asymptomatic for 30-60 min, consider increasing to 75%) back to 100% or to the maximum tolerated infusion rate. Continue to monitor the patient closely for any recurrent symptoms and administer additional antiemetic medications (i.e. rescue medication) as needed to manage symptoms effectively.

In patients with only nausea (no vomiting) during the first infusion, consider either making no modifications to the zolbetuximab infusion or stopping the infusion for 30-60 min and then restarting it at the same rate as before the stop if symptoms improve. After the first hour of the infusion (when the zolbetuximab dose is 800 mg/m^2 and the infusion is running at 200-265 mg/m^2/h), if the patient has only nausea (no vomiting), consider making no modifications to the zolbetuximab infusion, stopping the infusion for 30-60 min and restarting it at the same rate as before the stop if symptoms improve, or slowing the infusion without stopping it first.

In patients with only nausea (no vomiting) during second or subsequent infusions, consider first slowing the zolbetuximab infusion without stopping it or, if this is ineffective, stopping it and then restarting it at the rate before stop or at a slower rate.

The panel recommends against a decision to discontinue zolbetuximab permanently in patients experiencing nausea and vomiting without first attempting to modify the infusion rate and/or to escalate nausea and vomiting treatment. In patients with one or fewer episodes of vomiting, do not stop the infusion without attempting to restart it (i.e. do not withhold the dose).

We recommend treating patients experiencing nausea and vomiting with an antiemetic not used previously (e.g. lorazepam, olanzapine, metoclopramide, or levosulpiride outside of the United States). I.v. antiemetics are preferred in patients actively experiencing nausea and vomiting. I.v. hydration should be given to patients experiencing repeated vomiting; it may be appropriate to do so in select patients with fewer symptoms. In patients with refractory nausea or vomiting where premedication options have been escalated, scopolamine patch may be considered.

Planning for second or subsequent zolbetuximab infusions. The panel recommends the following adjustments for second or subsequent infusions based on the patient's symptoms during prior infusions:

- In patients with repeated vomiting, plan to infuse zolbetuximab at an infusion rate slower than that recommended in the PI and escalate the prophylactic regimen.
- In patients with one episode of vomiting, plan to infuse zolbetuximab at the rate recommended in the PI and escalate the prophylactic regimen.
- In patients with only nausea (no vomiting) who received their first infusion at the PI rate, plan to infuse zolbetuximab at the rate recommended in the PI and either provide the same prophylactic regimen or add additional agents.
- In patients with only nausea (no vomiting) who received their first infusion at a slower rate, plan to infuse zolbetuximab at the same slower rate and either provide the same prophylactic regimen or add additional agents.

In general, do not plan to stagger the zolbetuximab and chemotherapy regimens (i.e. give them 1 day to 1 week apart), unless the patient has experienced repeated vomiting during prior zolbetuximab infusions, in which case you may consider it. Overall, zolbetuximab infusions can be slowed and completed within a maximum window of 6 h; if the zolbetuximab infusion has been slowed to the point at which chemotherapy cannot be completed on the same day, chemotherapy can be provided the following day.

Additional general guidance. Provide patients and clinic staff with education regarding what symptoms to expect during each infusion and how to manage them at home.

We recommend antiulcer medications, such as a proton pump inhibitor or a histamine-2 receptor blocker, or antacids for patients with dyspepsia who have not had a prior total gastrectomy.

We encourage users of the guidance to discuss and utilize palliative care and other nonpharmacological options available if they are of interest to the patient.

DISCUSSION

Understanding toxicities and managing AEs associated with new agents is critical to improve real-world clinical practice and optimize patient care. In this study, we developed guidance for the prevention and management of nausea and vomiting in patients treated with zolbetuximab plus chemotherapy by utilizing a global expert panel with experience managing patients treated with zolbetuximab in clinical trials and the validated Delphi consensus methodology.

In SPOTLIGHT and GLOW, first-line zolbetuximab plus chemotherapy showed a clinically meaningful survival

benefit for patients with HER2-negative, locally advanced unresectable or metastatic G/GEJ adenocarcinoma whose tumors were CLDN18.2-positive.[7,8] Although advances in antiemetics have greatly decreased the incidence of chemotherapy-induced vomiting,[20] in SPOTLIGHT and GLOW, many patients still experienced nausea and vomiting despite the use of antiemetics.[7,8] Thus, an important impetus for this work was to advance the antiemetic guidance from SPOTLIGHT and GLOW further using the Delphi method, which has been used to achieve expert consensus to inform management of AEs.[21]

In this study, the Delphi panelists discussed interventions that may help to mitigate nausea and vomiting associated with zolbetuximab; they agreed that, before the first zolbetuximab infusion, NCCN-recommended treatment options for high-emetic-risk regimens should be used prophylactically irrespective of whether patients have a high or low risk of chemotherapy-induced nausea and vomiting, and whether or not they have had a prior total gastrectomy. Zolbetuximab should not be discontinued permanently without first attempting to modify or temporarily interrupt the infusion and/or without providing additional treatment for nausea and vomiting in the absence of hypersensitivity reactions or infusion-related reactions. While discontinuing zolbetuximab should be avoided, clinicians should retain flexibility for individual patient management. Depending on patient symptoms of nausea and/or vomiting, recommendations include modifying the zolbetuximab infusion rate, interrupting zolbetuximab infusions temporarily for 30-60 min, administering antiemetic medications not used for prophylaxis, and/or providing i.v. hydration. Patients and clinic staff should be educated, and it should be highlighted that nausea and vomiting will likely improve after the first zolbetuximab infusion and with subsequent infusions.

Strengths of the study included the use of an expert panel with diverse geographic, demographic, and institutional variables. The panel was representative of medical oncologists, as well as nurse practitioners and pharmacists. Additionally, all panelists completed two rounds of surveys and provided their responses without missing data. Finally, the study utilized the RAND/UCLA modified Delphi panel technique, which has been shown to be a reliable method for building consensus around clinical issues and has been widely used to develop clinical guidelines.[17] This study also has some limitations consistent with the use of the Delphi technique. Despite using a diverse panel with considerable experience, 15 panelists may not represent the experience of all providers in the field. Given the novelty of zolbetuximab as a first-in-class monoclonal antibody targeting CLDN18.2, only limited literature was available and reviewed on the prevention and management of nausea and vomiting with zolbetuximab treatment. Thus, to ensure the guidance remains current and informed by the latest data, iteratively updated guidelines are needed as new evidence from real-world studies becomes available. Finally, every clinical situation is different, and these guidelines may not capture all possible clinical scenarios. Physicians should continue to apply their clinical expertise and refer to institutional protocols and guidelines to manage the general disease and nausea and vomiting associated with chemotherapy. The guidance should be used for reference and should not supersede physician decision making.

Conclusions

Consensus-based guidelines informed by published literature and clinical experience were developed. These recommendations, for the prevention and management of nausea and vomiting in patients treated with zolbetuximab plus chemotherapy, can be utilized by clinicians in their decision making and may help them to provide improved patient care.

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DISCLOSURE

SJK reports receiving consulting fees from Astellas Pharma and Novartis; receiving honoraria from Merck Sharp & Dohme; serving a consulting or advisory role for Amgen, Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Coherus BioSciences, Daiichi Sankyo, Eisai, I-Mab, Merck Sharp & Dohme, Mersana, Natera, Novartis, Pfizer, Sanofi-Aventis, and Servier; serving as a committee member of the NCCN; and previously owning stocks from Nuvalent and Turning Point Therapeutics. RAPC reports receiving personal honoraria as an invited speaker from Amgen, Astellas Pharma, Bristol Myers Squibb, Eisai, Eli Lilly, and Roche; receiving payment for expert testimony from AstraZeneca, Bristol Myers Squibb, and Eli Lilly; receiving support for travel and/or meeting attendance from Astellas Pharma, Bristol Myers Squibb, Eli Lilly, and Roche; and participating on data safety monitoring boards or advisory boards for AstraZeneca, Ipsen, and Roche. SL reports receiving research funding (to institution) from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, Merck Serono, and Roche; receiving personal honoraria as an invited speaker from Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Incyte, Merck Serono, Merck Sharp & Dohme, Pierre Fabre, Roche, and Servier; participating in advisory boards for Amgen, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Incyte, Merck Serono, Merck Sharp & Dohme, Rottapharm Biotech, Servier, and Takeda; and serving as a member of the Gruppo Oncologico Nord Ovest (GONO) Foundation. LS reports receiving payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Astellas Pharma, Horizon CME, and Pfizer; and receiving support for

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