Factors affecting the implementation of guideline-based prophylactic antiemetic therapy for chemotherapy-induced nausea and vomiting in Japan: a protocol for a hospital-based qualitative study

Akiko Yaguchi-Saito,1,2 Yuki Kaji,1 Ayumu Matsuoka,1 Ayako Okuyama,3,4 Maiko Fujimori,1 Junko Saito,1,5 Miyuki Odawara,1 Aki Otsuki,1 Yosuke Uchitomi,1 Sadamoto Zenda,5 Taichi Shimazu1

ABSTRACT

Introduction Chemotherapy-induced nausea and vomiting (CINV) decrease patients’ quality of life and negatively impact treatment outcomes. Although standard prophylactic antiemetic therapy for acute CINV recommended by guidelines is effective, poor guideline implementation is a worldwide problem. In Japan, prophylactic antiemetic therapy is relatively well implemented for chemotherapy associated with high emetogenic risk, while implementation gaps are observed for that with low emetogenic risk. Although most reports on factors influencing appropriate antiemetic prescription focus on physicians’ attitudes and behaviours, a more comprehensive exploration is needed since chemotherapy is expected to involve pharmacists, nurses and eventually hospital directors. The purpose of this qualitative study is to comprehensively explore the factors that influence the implementation of appropriate prophylactic antiemetic procedures at cancer care hospitals in Japan.

Methods and analysis This study is a hospital-based qualitative study using semistructured individual interviews. The target population will be hospital directors, and chiefs (including proxies) of departments of oncology and/or chemotherapy, pharmacy and nursing, working in the hospitals, selected by purposive sampling. We will obtain information on antiemetics in chemotherapy regimens, antiemetic routine use and awareness of guidelines using prequestionnaires. Interviews will then be conducted online using an interview guide. The development of chemotherapy-induced nausea and vomiting (CINV) decreases the quality of life of patients with cancer, making the continuation of treatment difficult1–3 and increasing the overall cost of cancer care.4

In Europe and the USA, international standards for antiemetic therapies for CINV have been published as practice guidelines.5–7 In Japan, the Japan Society of Clinical Oncology...
published the Guidelines for Appropriate Antiemetic Prophylaxis,8 which are unique and complementary to the European and American guidelines and are useful in adapting to the Japanese medical situation and include prescribable antiemetic drugs.9 These guidelines classify chemotherapy into four levels according to the risk of emetogenicity of the drugs used: highly emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), low-emetogenic chemotherapy (LEC) and minimally emetogenic chemotherapy.5–8 Recommendations for prophylactic antiemetic therapy for CINV are provided per risk category.

Implementation gap in prophylactic antiemetic therapies
For initial anticancer therapy, prophylactic antiemetic therapy according to emetic risk should basically be commenced with the prescription recommended in the guidelines, and its effectiveness has been reported.9–11 However, implementation of those recommendations has been reported to be inadequate worldwide.10 12–17 Implementation of prophylactic antiemetic therapies recommended in the guidelines for HEC is relatively low (<30%) in the USA18 and Europe.13 16 In contrast, two nationwide surveys11 17 on the use of prophylactic antiemetics for patients receiving HEC in Japan have shown that the recommended three-drug combination (serotonin-3 receptor antagonist (5HT3RA), dexamethasone (Dex) and neurokinin-I receptor antagonist (NK1RA)) was administered in approximately 60% and 74% of patients, respectively, within 3 years of the guidelines’ publication in 2010, suggesting widespread use of appropriate antiemetic therapy.

In contrast, an overuse of antiemetic agents prescribed prophylactically for LEC has been noted worldwide,14 15 18 including in Japan, where the combination of Dex and a 5HT3RA was prescribed for approximately half of eligible patients, despite the recommendation to use a single-agent.14 In this study, we chose antiemetic therapies for HEC and LEC and their antiemetic therapies as markers for appropriate use and overuse, respectively. MEC was excluded from this study because the anticancer drugs classified as MEC differ between Japan and other countries; and there are some variations in the appropriate antiemetic drugs for each MEC.19

Factors affecting the guideline-based implementation of prophylactic antiemetic therapy
Evidence is scarce on the factors (ie, barriers and facilitators) affecting the discrepancies between recommended and implemented effective antiemetic therapy. In their review,26 Bierbaum et al identified facilitators of physicians’ adherence to guidelines for cancer treatment, including the accessibility and ease of use of clinical practice guidelines (CPGs), endorsement and dissemination of CPGs, adequacy of access to treatment facilities, awareness of CPGs and belief in the relevance of CPGs. Surveys conducted in the USA21 and Europe22 showed that oncology nurses perceived physicians’ preference, physicians’ satisfaction with current treatment, insurance coverage for antiemetics and medications on formularies as the factors influencing the implementation of antiemetic guidelines.

However, chemotherapy in hospitals of medium or larger size may involve considerations regarding physicians, nurses and pharmacists, as well as interprofessional workers and hospital-based prescription processes. Iihara et al23 reported that the proactive involvement of pharmacists in antiemetic therapy improved the quality of medical practices. In addition, in many Japanese hospitals, nurses may receive direct patient requests during risk assessment and management of CINV. Furthermore, the influence of the head of the institution as the hospital supervisor may be important. Leadership support, such as commitment and active interest in practice implementation, creates a stronger implementation climate, which leads to implementation effectiveness.24

At a hospital system level, the impact of chemotherapy should also be considered if it is delivered as a regimen through a computerised prescription/physician order entry (CPOE) system. CPOE systems may reduce medication errors, increase medical safety for patients and improve the integrity of chemotherapy documentation and medical record.25 26 Kadakia et al27 reported that CPOE systems were associated with adherence to institutional guidelines for antiemetic use. However, in order for CPOE to be of practical use, adequate regimens must be included in the CPOE of the hospitals. To achieve this, regimen management, including approval and registration of regimens for anticancer and antiemetic drugs, as well as the elimination of old regimens, may also be considered at each hospital.

Our study will provide a unique opportunity to elucidate factors affecting the implementation of guideline-based prophylactic antiemetic therapy in hospitals providing chemotherapy with regimens on the CPOE system. In Japan, the Ministry of Health, Labour and Welfare (MHLW) has assigned ‘Designated Cancer Care Hospitals’ (DCCHs) as part of cancer control measures aimed at providing high-quality cancer care anywhere in Japan, based on several requirements, including the assignment of specialists for cancer treatment, multidisciplinary cooperation and establishment of committees for regimen management. As of April 2021, there are 405 DCCHs. From 2005 to 2011, approximately half of the patients who received initial chemotherapy for major cancers (stomach, colon, liver, lung and breast) were treated at DCCHs.28 In addition, an estimated 80% of hospitals with more than 200 beds are equipped with CPOE systems.29 This means that CPOE systems are present at most DCCHs. Insights into factors affecting the implementation of guideline-based prophylactic antiemetic therapy among healthcare providers, institution heads and hospital systems at interindividual and organisational levels, as well as at the societal level, including institutions, are required.
Aims of the study
The aim of this study is to comprehensively examine factors affecting the implementation of guideline-based prophylactic antiemetic therapy at the time of initial administration of anticancer drugs.

METHODS AND ANALYSIS

We will undertake a hospital-based qualitative study using semistructured individual interviews with physicians, pharmacists, nurses and hospital directors, as well as a review of documentation regarding regimen management. A brief questionnaire survey will be administered prior to the interviews; we will refer to aggregate results of health utilisation data linked to the hospital-based cancer registry to evaluate the implementation of antiemetic prophylaxis in hospitals.

Conceptual framework
To identify influencing factors and explain the nature of their influence on the implementation of antiemetic therapy based on the Japan Society of Clinical Oncology antiemetic guidelines,8 we will use the Consolidated Framework for Implementation Research (CFIR).24 This framework consists of 39 constructs organised into the five domains: intervention characteristics, outer setting, inner setting, characteristics of individuals and process, and is used to identify existing or potential barriers and facilitators to the implementation of evidence-based interventions in healthcare settings in relevant contexts.30 For the current study, we will use this framework to collect and analyse interview-based and document-based data.

Sampling and recruitment
The inclusion criteria for the target hospitals in this study are DCCHs. We will use purposive sampling and snowball sampling to recruit participant hospitals according to hospital type (cancer centres, university hospitals and general hospitals) and region (urban or rural), and one or two hospitals in each segment will be selected; however, additional recruitment will be conducted if the information is not saturated. We have begun to send requests for participation to some hospital directors, explaining the purpose of our study and requesting that they return contact information for participant interviews. Semistructured interviews will be conducted with the hospital director, chief or alternate members of the departments of breast, gastrointestinal, thoracic, and/or medical oncology and chiefs or subchiefs of the departments of pharmacy and nursing. The reason for including the three departments (breast, gastrointestinal and thoracic oncology) in this study is that implementation of guideline-recommended antiemetic therapy for HEC for cancer types treated in these departments were high,19 potentially helping to clarify the factors that affect the implementation of guideline-recommended antiemetic therapy for LEC. We have scheduled interviews with 35–40 people at a total of 10–15 hospitals.

Preinterview questionnaires and document review
Before interviewing respective physicians and pharmacists, we will send and collect preinterview questionnaires by e-mail. In the questionnaire, we will inquire about the tenure of the interviewees, the number of specialists in the department, regimen registry and routine prescription of prophylactic antiemetics for the first administration of chemotherapy with high and low emetic risk during an acute phase. Furthermore, we will ask about access and reference to the antiemetic therapy guidelines (table 1). In addition, we will ask the interviewees from each department of pharmacy to provide documentation relevant to regimen management, such as the committee’s code for regimen management or the institution’s guidelines for antiemetic therapy.

Semi-structured interviews
Interview guides have been developed as open questions that follow the process of antiemetic regimen registration and prescribing (per regimen), and interrogate the factors affecting regimen implementation. For the barriers and facilitators, probe questions will be added with CFIR constructs in consideration. The draft of the interview guide was revised after pilot interviews were conducted with three oncologists, a pharmacist, a nurse and a hospital director. Table 1 presents a summary of the finalised interview guides.

Interviews will be conducted online, with AVS (PhD, MPH, project researcher) as the interviewer, and TS (PhD, MD, principal investigator), YK (MPH, MD, project researcher) and AM (PhD, MD, project researcher) will attend, as needed. The interviews will last 20–30 min each for hospital directors and 40–50 min each for other healthcare professionals, considering the time constraints of the participants. With participant permission, we will extend the interview to approximately 60 min. In the beginning, we will explain the purpose of the interview. After obtaining participant permission, we will record the interview. There will be no compensation for the interviewees. At each hospital, an interview with the hospital director will be conducted last. At the end of the interview, we will provide a ‘Consent Form for Referencing Quality Indicator (QI) Survey Results’ and request participant consent to our use of their aggregate results to the QI survey to evaluate the implementation of antiemetic treatment for HECs and LECs in the examined hospitals. At the closing of the interview, the interviewer and participating researchers will conduct a brief review of the interview and discuss the points of interest.

The transcription of audio recordings of all interviews will be outsourced to a service provider. The names of the hospitals and participants will be removed, and AVS will check all transcriptions for accuracy. Any unclear statements will be checked with the interviewee or researcher in attendance at the interview, as required.
Table 1  Summary of preinterview questionnaire and interview guide for semistructured interviews

| Interviewee                  | Preinterview questionnaire Topics                                                                 | Semistructured interviews Topics                                                                 | Example questions                                                                 |
|------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Director                     | Hospital policy and leadership on evidence-based medicine, regimen management, supportive care |                                                                                                   | What is the hospital’s policy on the overall implementation of supportive care based on (and utilising) the recommendations of medical guidelines?  |
| Chief of Department of Oncology | ‣ Number of members and specialties of the department ‣ Reference to CPG ‣ Antiemetics on chemotherapeutic regimen, routinely prescribed prophylactic antiemetics | Regimen management                                                                                     | When and how was your hospital’s regimen registration and management system developed? |
|                              |                                                                                                   |                                                                                                   | What are the advantages and disadvantages of your current regimen registration and management system? |
|                              |                                                                                                   |                                                                                                   | How is the director involved in the management of regimen registration?          |
| Antiemetic guidelines        |                                                                                                   |                                                                                                   | What do you think of the recommendations in the antiemetic guidelines?           |
|                              |                                                                                                   |                                                                                                   | When do you refer to the antiemetic guidelines?                                 |
| Patient needs regarding antiemetics |                                                                                                   |                                                                                                   | How do you explain CINV to patients?                                            |
|                              |                                                                                                   |                                                                                                   | What kind of answers or questions do you receive from patients?                |
| Regimen of antiemetic prophylaxis for LEC |                                                                                                   |                                                                                                   | How did the regimen come to be registered?                                    |
|                              |                                                                                                   |                                                                                                   | What evidence was considered at registration?                                 |
| Factors influencing appropriate antiemetic therapy |                                                                                                   |                                                                                                   | What do you think is the status of the implementation of antiemetic use in your hospital? |
|                              |                                                                                                   |                                                                                                   | What do you think is the reason for this?                                     |
| Chief of Department of Pharmacy | ‣ Number of members and specialties of the department ‣ Regimen management ‣ Confirmation of antiemetic prescription ‣ Standardisations of regimen in the hospitals ‣ Reference to CPG | Regimen of antiemetic prophylaxis for LEC                                                                 | How did the regimen come to be registered?                                    |
|                              |                                                                                                   |                                                                                                   | What evidence was considered at registration?                                 |
| Antiemetic guidelines        |                                                                                                   |                                                                                                   | What do you think of the recommendations in the antiemetic guidelines?           |
|                              |                                                                                                   |                                                                                                   | How do you explain CINV to patients?                                            |
| Patient needs regarding antiemetics |                                                                                                   |                                                                                                   | What kind of answers or questions do you receive from patients?                |
|                              |                                                                                                   |                                                                                                   | How do you explain CINV to patients?                                            |
| Factors influencing appropriate antiemetic therapy |                                                                                                   |                                                                                                   | What do you think is the status of the implementation of antiemetic use in your hospital? |
|                              |                                                                                                   |                                                                                                   | What do you think is the reason for this?                                     |
| Chief of Department of Nursing |                                                                                                   |                                                                                                   | How do you explain CINV to patients?                                            |
|                              |                                                                                                   |                                                                                                   | What kind of answers or questions do you receive from patients?                |
| Factors influencing appropriate antiemetic therapy |                                                                                                   |                                                                                                   | What do you think is the status of the implementation of antiemetic use in your hospital? |
|                              |                                                                                                   |                                                                                                   | What do you think is the reason for this?                                     |

CINV, chemotherapy-induced nausea and vomiting; CPG, clinical practice guidelines; LEC, low-emetogenic chemotherapy.

Analysis
The interviews will be conducted, following a qualitative content analysis procedure:
1. AY-S, YK, AM and TS will discuss the content to be coded in each CFIR construct.
2. For the first two interviewees, coders (AY-S, YK and AM) will independently deduce and code each CFIR construct in the corresponding section of the transcript. If the corresponding code is unclear, the section will be open-coded and labelled.
3. AY-S, YK and AM will compare and discuss the results of the codes and make a codebook with tentative definitions for each construct in the context of this study.
4. For other interview transcripts, coders will independently code constructs according to the codebook, and the results will be collated, discussed and agreed on. As the analysis progresses, the codebook will be expanded, as required.

5. In addition, we will use the qualitative data software package NVivo V.12 software (QSR International, Melbourne, Australia) to collect similar descriptions coded in each construct and determine a definition for each construct. Content that cannot be coded in any of the constructs will be inductively coded as a new construct the authors will create.

6. Diagrams showing the relationships among the constructs will be drawn for each hospital to gain a comprehensive understanding of influencing factors. We will also prepare a summary memo for each hospital, organising it along with the constructs of the CFIR.

7. In the process of creating the related diagrams and summary memos, we will refer to the aggregate results on the degree of implementation (QI survey) and will verify their relationship to the constructs.

Degree of implementation of prophylactic therapy

To determine the degree of implementation of prophylactic antiemetic therapy in the relevant hospitals, we will refer to the aggregate results of a survey on antiemetic therapy conducted as a part of the QI survey commissioned by the Ministry of Health, Labour and Welfare. In this survey, healthcare utilisation data linked to hospital cancer registries of 436 hospitals, including 302 DCCHs, will be analysed, and patients diagnosed with cancer in 2016 and treated with chemotherapy for the first time at the selected hospitals will be included. We will refer to the percentages of the patients diagnosed with gastric, colorectal, oesophageal, lung and breast cancers who received HEC and prophylaxis with three drugs (5HT, RA, NK, RA and Dex), as well as the percentage of patients who received LEC and several possible antiemetic prescription patterns. The mean and quartile values of all facilities per prescription percentage will also be referenced. The aggregate results will be triangulated with qualitative data, accounting for the background of patients in each hospital, such as age and type of cancer.

Patient and public involvement

A cancer survivor (30s) is participating as a research collaborator, attended a meeting to discuss the research plan and commented on the concept of the study.

Study period

The first interview was conducted on 2 November 2020. The analysis will be completed in 30 June 2022.

ETHICS AND DISSEMINATION

This study has been approved by the National Cancer Centre Ethics Approval Committee (approval number: 2020-305). Participation in this study will be voluntary, and interviews will be conducted on acquiring verbal consent.

Dissemination of study findings

Study findings will be disseminated via peer-reviewed journal publications and presentations to the public, academics, policy-makers and clinicians at scientific conferences.

Author affiliations

1. Division of Behavioral Sciences, National Cancer Center Institute for Cancer Control, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan
2. Faculty of Human Sciences, Tokiwa University, 1-430-1, Miwa, Mito-shi, Ibaraki, 310-8585, Japan
3. Center for Cancer Control and Information Services, National Cancer Center Japan, Chuo-ku, Tokyo, 104-0045, Japan
4. Graduate school of Nursing Science, St. Luke’s International University, 10-1 Akashi-cho, Chuo-ku, Tokyo, 104-0044, Japan
5. Radiation Oncology, National Cancer Center-Hospital East, Kashiwa, Chiba, 277-8577, Japan

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Contributors

SZ, TS and AY-S conceived the study, SZ, TS, AY-S, YK, AM, AOK, MF, JS, MD, YU and AOT contributed significantly to the design. AY-S drafted the paper, ST, AOK, AS, YK, AM, MF, MD, YU and AOT revised the paper critically for important intellectual content. All authors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interests

None declared.

Patient and public involvement

Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

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ORCID iDs

Akiko Yaguchi-Saito http://orcid.org/0000-0003-2391-5804
Ayako Okuyama http://orcid.org/0000-0003-4732-3272
Maiko Fujimori http://orcid.org/0000-0003-1639-3390
Junko Salo http://orcid.org/0000-0002-6923-7298
Sadamoto Zenda http://orcid.org/0000-0002-0421-5805
Taichi Shimazu http://orcid.org/0000-0001-6000-9830

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