Japanese Society of Clinical Oncology clinical practice guidelines 2010 for antiemesis in oncology: executive summary

Hideki Takeuchi1,2 · Toshiaki Saeki2 · Keisuke Aiba3 · Kazuo Tamura4 · Kenjiro Aogi5 · Kenji Eguchi6 · Kenji Okita7 · Yoshikazu Kagami8 · Ryuhei Tanaka9 · Kazuhiko Nakagawa10 · Hirofumi Fujii11 · Narikazu Boku12 · Makoto Wada13 · Tatsuo Akechi14 · Yasuhiro Udagawa15 · Yutaka Okawa8 · Yusuke Onozawa16 · Hidenori Sasaki17 · Yasuo Shima18 · Naohito Shimoyama19 · Masayuki Takeda10 · Toshihiko Nishidate7 · Akifumi Yamamoto20 · Tadashi Ikeda21 · Koichi Hirata7

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Abstract The purpose of this article is to disseminate the standard of antiemetic therapy for Japanese clinical oncologists. On the basis of the Appraisal of Guidelines for Research and Evaluation II instrument, which reflects evidence-based clinical practice guidelines, a working group of the Japanese Society of Clinical Oncology (JSCO) reviewed clinical practice guidelines for antiemesis and performed a systematic review of evidence-based domestic practice guidelines for antiemetic therapy in Japan. In addition, because health-insurance systems in Japan are different from those in other countries, a consensus was reached regarding standard treatments for chemotherapy that induce nausea and vomiting. Current evidence was collected by use of MEDLINE, from materials from meetings of the American Society of Clinical Oncology National Comprehensive Cancer Network, and from European Society of Medical Oncology/Multinational Association of Supportive Care in Cancer guidelines for antiemesis. Initially, 21 clinical questions (CQ)
were selected on the basis of CQs from other guidelines. Patients treated with highly emetic agents should receive a serotonin (5-hydroxytryptamine; 5HT₃) receptor antagonist, dexamethasone, and a neurokinin 1 receptor antagonist. For patients with moderate emetic risk, 5HT₃ receptor antagonists and dexamethasone were recommended, whereas for those receiving chemotherapy with low emetic risk dexamethasone only is recommended. Patients receiving high-emetic-risk radiation therapy should also receive a 5HT₃ receptor antagonist. In this paper the 2010 JSCO clinical practice guidelines for antiemesis are presented in English; they reveal high concordance of Japanese medical circumstances with other antiemetic guidelines that are similarly based on evidence.

Keywords Antiemetic treatment · Cancer chemotherapy · Clinical practice guideline

Introduction

Recent developments in cancer chemotherapy have improved the survival of patients with a variety of malignancies. However, antiemetic treatments for chemotherapy which induce nausea and vomiting (CINV) are critical for successful chemotherapy. Consensus and/or evidence-based guidelines for antiemetic treatment in oncology have been issued by the National Comprehensive Cancer Network (NCCN) [1], the Multinational Association of Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO) [2], and the American Society of Clinical Oncology (ASCO) [3]. However, application of these guidelines in Japan is limited because of different clinical circumstances and different domestic insurance coverage. Hence the Japanese clinical practice guideline for antiemetics was established and published on May 1st, 2010 as the first publication of the Japanese Society of Clinical Oncology (JSCO).

Methods

Initially, JSCO selected members of a working group for these guidelines on the basis of the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [4], which assesses the methods used to generate evidence-based clinical practice guidelines. The members of a working group were included medical oncologists, oncological surgeons, palliative care physicians, and psycho-oncologists. The AGREE II Instrument is available as a PDF or in electronic form from http://www.agreetrust.org/resource-centre/agree-ii/. A draft of the guidelines was developed systematically, and members of the medical staff were in unanimous agreement with regard to all recommendations for treatment and clinical questions (CQ). However, domestic factors including ethnicity and health policy formation at the system level required further consideration. Hence, a consensus of all medical practitioners was held at a consensus meeting, and recommendations for antiemetic treatments were discussed in the context of Japanese medical circumstances.

Literature search strategy

A systematic review and meta-analysis of the effectiveness of antiemetic therapy was performed by use of the major international guidelines NCCN, MASSC/ESMO, and ASCO as sources of information [1–3]. Subsequently, high-level evidence was selected from the literature, and structured abstracts were generated for each of the manuscripts included. MEDLINE searches were also performed to identify other randomized controlled trials, and the Cochrane library was reviewed during 2008–2010 [5]. Materials from ASCO and MASSC annual meetings were reviewed and some Japanese manuscripts containing sufficiently strong evidence were included. Materials that were available in abstract form only were not considered.

Inclusion criteria for published studies

Systematic reviews and reports of randomized controlled trials were included if the intervention was for treatment of nausea or vomiting after cancer therapy, and nausea and/or vomiting outcomes were reported. This guideline was reviewed and approved by the JSCO Clinical Practice Guidelines Committee and the Board of Directors, and was reviewed and approved for publication in the International Journal of Clinical Oncology.

Guidelines and conflicts of interest

The Update Committee was assembled in accordance with ASCO’s Conflict of Interest (COI) Management Procedures for Clinical Practice Guidelines (“Procedures”, summarized at http://www.asco.org/guidelinescoi). The members of the working group provided disclosure forms that required disclosure of financial and other interests to the board of directors of JSCO. Subsequently, the COI

20 Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Saitama, Japan
21 Department of Surgery, Teikyo University School of Medicine, Tokyo, Japan
committee reviewed the COI of each member and allowed all members without COIs to contribute to the guideline.

**Recommendation grade**

Recommendation grades were stated as follows:

- **A**: Strongly recommended clinical action
- **B**: Recommended clinical action
- **C1**: Clinical action may be useful although there is a lack of high-level scientific evidence
- **C2**: Not recommended because of insufficient scientific evidence
- **D**: Clinical action not recommended

**Results**

The working group of JSCO clinical practice guidelines for antiemesis adopted a clinical question (CQ) form as the main guideline format and selected the following 21 CQs:

CQ1. How is the emetic risk induced by cancer chemotherapy categorized?

Recommendation (Grade A): the emetic risk induced by cancer chemotherapy is classified as high, moderate, low, and minimum according to the frequency of patient nausea and vomiting experiences, and antiemetic prophylactic treatments are prescribed in accordance with these categories.

The emetic risks of cancer chemotherapy depend on the potential emetogenicity of combined chemotherapeutic regimens. The emetic risk is evaluated on the basis of the percentage of untreated patients who experience acute emesis within 24 h of initiation and/or administration of cancer chemotherapy and is categorized as follows:

- **High emetic risk**: 90% or more patients experience acute emesis
- **Moderate emetic risk**: 30–90% of patients experience acute emesis
- **Low emetic risk**: 10–30% of patients experience acute emesis
- **Minimum emetic risk**: fewer than 10% of patients experience acute emesis

CQ2. How are intravenous chemotherapeutic agents categorized for the emetic risk?

Recommendation (Grade A): proper and sufficient antiemetic prophylaxis should be recommended in accordance with the four risk categories (Table 1).

Recommendation (Grade C1): antiemetic treatments for domestic chemotherapeutic agents developed in Japan are uncertain because of limited evidence of drug efficacy and low frequency of usage.

Emetic risks of chemotherapeutic agents are classified in Table 1 on the basis of the recommendations of existing guidelines produced with a high level of consensus, for example NCCN, MASSC, and ASCO; they were modified in consideration of particular clinical circumstances in Japan [6, 7]. Most chemotherapeutic regimens with high or moderate emetic risk include intravenous chemotherapeutic agents, and proper and flexible management of their emetic risks is essential because they are usually administered over several days and include several drugs. Although the 2009 NCCN guidelines indicate that high and low-dose cisplatin regimens have high and moderate emetic risk, respectively, the 2008 MASCC and 2006 ASCO guidelines categorized cisplatin as a drug of high emetic risk irrespective of dosage [8, 9]. Accordingly, all cisplatin regimens, including those administered over several days were regarded as regimens of high emetic risk (CQ10). However, combined regimens that include anthracycline and cyclophosphamide, for example AC, CAF, EC, and FEC, are usually regarded as having high emetogenicity. The 2009 NCCN guidelines categorized these anthracycline-containing regimens as high emetic risk similar to other monotherapeutic agents with high emetogenicity. Hence, this categorization was used for all anthracycline-containing regimens.

CQ3. How are the emetic risk categories for oral chemotherapeutic agents defined and managed?

Recommendation (Grade C1): according to clinical study protocols designed to assess efficacy as supportive co-treatments, suspension and/or dose reduction of chemotherapeutic agents should be considered to limit nausea and vomiting to grade 3 or less.

The emetic risk of oral chemotherapeutic agents is listed in Table 2. In Japan, oral fluoropyrimidine-based regimens are frequently used as adjuvant treatments with tegafur-uracil and/or leucovorin and capetitabine for colorectal cancer, S-1 for gastric cancer, and tegafur-uracil for breast and lung cancers, and several clinical trials have demonstrated efficacy is reasonable. Moreover, the Japanese clinical practice guidelines have indicated that S-1 and tegafur-uracil and/or leucovorin are efficacious treatment strategies for advanced gastric and colorectal cancers. Although these oral chemotherapeutic agents have lower emetogenicity when administered alone, adverse digestive events occur after repeated daily administration. Hence, antiemetic treatments are important to achieving higher drug adherence and to optimizing treatment.

CQ4. How should acute nausea and vomiting induced by cancer chemotherapy be prevented?

Recommendation (Grade A): a triple regimen of neurokinin 1 (NK1) receptor antagonist (aprepitant), serotonin (5-hydroxytryptamine: 5HT3) receptor antagonist, and dexamethasone is recommended for acute emesis during highly emetic cancer chemotherapy.
Recommendation (Grade A): regimens containing 5HT\textsubscript{3} receptor antagonists and dexamethasone are basically recommended for acute emesis during moderately emetic cancer chemotherapy. For particular chemotherapeutic regimens, addition of an NK1 receptor antagonist to regimens of 5HT\textsubscript{3} receptor antagonist and dexamethasone are considered.

### Table 1 Emetic risk category for intravenous chemotherapeutic agents

| JSCO emetic risk category                      | Agent (regimen)       |
|-----------------------------------------------|-----------------------|
| High emetic risk (emetic frequency >90 %)      |                       |
| Cisplatin                                     |                       |
| Cyclophosphamide (>1500 mg/m\textsuperscript{2}) |                       |
| Dacarbazine                                   |                       |
| Doxorubicin + cyclophosphamide                |                       |
| Epirubicin + cyclophosphamide                 |                       |
| Altretaine                                    |                       |
| Carmustine (>250 mg/m\textsuperscript{2})     |                       |
| Mechlorethamine                               |                       |
| Streptozocin                                   |                       |
| Moderate emetic risk (emetic frequency 30–90 %) |                       |
| Actinomycin D                                 |                       |
| Amrubicin                                     |                       |
| Arsenic trioxide                              |                       |
| Busulfan (>4 mg/day)                          |                       |
| Carboplatin                                   |                       |
| Cyclophosphamide (<1500 mg/m\textsuperscript{2}) |                       |
| Cytoxarbine (>200 mg/m\textsuperscript{2})    |                       |
| Daunorubicin                                  |                       |
| Doxorubicin                                   |                       |
| Enocitabine                                   |                       |
| Epirubicin                                    |                       |
| Idarubicin                                    |                       |
| Iosphamide                                    |                       |
| Interferon α (<10 million IU/m\textsuperscript{3}) |                       |
| Interleukin-2 (12–15 million IU/m\textsuperscript{3}) |                       |
| Low emetic risk (emetic frequency 10–30 %)    |                       |
| Interleukin-2 (<12 million IU/m\textsuperscript{3}) |                       |
| Cytoxarbine (100–200 mg/m\textsuperscript{2})  |                       |
| Docetaxel                                     |                       |
| Etoposide                                     |                       |
| 5-Fluorouracil                                |                       |
| Gemcitabine                                   |                       |
| Interferon α (5–10 million IU/m\textsuperscript{3}) |                       |
| Liposomal doxorubicin                         |                       |
| Methotrexate (50–250 mg/m\textsuperscript{2})  |                       |
| Mitomycin C                                   |                       |
| Minimum emetic risk (emetic frequency: <10 %)  |                       |
| i-Asparaginase                                |                       |
| Bevacizumab                                   |                       |
| Bleomycin                                     |                       |
| Bortezomib                                    |                       |
| Cetuximab                                     |                       |
| Cladribine                                    |                       |
| Cytoxarbine (<100 mg/m\textsuperscript{2})     |                       |
| Fludarabine                                   |                       |
| Gemtuzumab ozogamicin                         |                       |
| Methotrexate (<50 mg/m\textsuperscript{2})     |                       |
| Nelarabine                                    |                       |
| Peplomycin                                    |                       |
| Rituximab                                     |                       |
| Vinblastine                                   |                       |
| Vincristine                                   |                       |
| Vinorelbine                                   |                       |
| Trastuzumab                                   |                       |
| Vindesine                                     |                       |
| Alectumuzumab                                 |                       |
| Decitabine                                    |                       |
| Denileukin difitox                            |                       |
| Dexrazoxane                                   |                       |
| Panitumumab                                   |                       |
| Pegaspargase                                  |                       |
| Tensirolimus                                  |                       |
| Vinrubin                                     |                       |

Agents in italics are not approved for clinical use in Japan
Acute onset of nausea and vomiting occurs within a few minutes to several hours, and intensity generally peaks from 5 to 6 h after administration of chemotherapy and usually recovers within 24 h. Management and control of CINV are essential for successful cancer chemotherapy, because unfavorable side effects of nausea and vomiting are associated with poor treatment adherence and effects. In addition, incomplete prevention of acute emesis may lead to uncontrollable delayed emesis [10]. Hence, according to the four emetic risk categories indicated in CQ2 and 3, appropriate and sufficient antiemetic treatments are needed from the start of chemotherapy. The standard model of antiemetic treatment regimens is detailed in the four diagrams in Fig. 1. In the high emetic risk diagram, evidence of antiemetic actions of AC regimens was taken from clinical trials of other highly emetic cancer agents, and suggests no additional effects of dexamethasone after day 2. Upon issue of the 1st guideline, oral aprepitant was the only NK1 receptor antagonist available for clinical use in Japan. Subsequently, in November 2011, the Japanese Ministry of Health, Labour, and Welfare approved the intravenous NK1 receptor antagonist, fosaprepitant. Accordingly, we immediately modified the diagram and included additional information about fosaprepitant as a minor revision of the guideline, with careful consideration of the limited evidence of its efficacy and safety.

CQ5. How should delayed nausea and vomiting after cancer chemotherapy be prevented?

Recommendation (Grade A): a combined regimen of NK1 receptor antagonist (aprepitant) and dexamethasone is recommended for treatment of delayed emesis during highly emetic cancer chemotherapy.

Recommendation (Grade A): single administration of dexamethasone is basically recommended for delayed emesis during moderately emetic cancer chemotherapy. However, regimens of NK1 antagonist and/or dexamethasone are considered.

Delayed onset of nausea and vomiting occurs later than 24 h after administration of chemotherapy. In these circumstances, control of delayed emesis is essential to maintaining patients’ quality of life and for motivating further treatment with a healthy mentality. As described in CQ4, complete prevention of acute emesis is the most important and fundamental strategy for preventing delayed emesis (Fig. 1). In specific cases in which dexamethasone should be restricted, 2–4 days of 5HT3 antagonist is recommended instead of dexamethasone.

CQ6. What kinds of serotonin (5HT3) receptor antagonist are available in Japan?

Recommendation (Grade A): 5HT3 receptor antagonists are effective treatments for prevention of nausea and vomiting during cancer chemotherapy; seven drugs are approved in Japan: granisetron, palonosetron, ramosetron, ondansetron, tropisetron, azasetron, and indisetron.

Several 5HT3 receptor antagonists are currently available in Japan, and efficacy for management of CINV has been demonstrated for all these agents, particularly under conditions of acute phase emesis. However, the efficacy of these agents for treatment of delayed emesis remains controversial because no further antiemetic effects of additional treatments have been observed after initial use.

Table 2  Emetic risk category for oral chemotherapeutic agents

| JSCO emetic risk category | Agent (regimen) |
|--------------------------|-----------------|
| High emetic risk (>90 %)  | Procarbazine    |
| Moderate emetic risk (30–90 %) | Cyclophosphamide, Etoposide, Imatinib |
| Low emetic risk (10–30 %) | Capecitabine, Doxifluoridine, Mercaptopurine, Nitotinib |
| Minimum emetic risk (<10 %) | Dasatinib, Erlotinib, Fludarabine, Gefitinib, Hydroxyurea, Lapatinib, Melphalan, Methotrexate |

Agents in italics are not approved for clinical use in Japan.

| CQ2 | 5HT3 receptor antagonists are effective treatments for prevention of nausea and vomiting during cancer chemotherapy; seven drugs are approved in Japan: granisetron, palonosetron, ramosetron, ondansetron, tropisetron, azasetron, and indisetron. |
| CQ4 | Several 5HT3 receptor antagonists are currently available in Japan, and efficacy for management of CINV has been demonstrated for all these agents, particularly under conditions of acute phase emesis. However, the efficacy of these agents for treatment of delayed emesis remains controversial because no further antiemetic effects of additional treatments have been observed after initial use. |
of 5HT₃ receptors with antagonistic agents. It has been proved that palonosetron is not inferior to granisetron in the acute phase and is superior to granisetron in the delayed phase [11].

CQ7. What is the recommended dose of corticosteroid for antiemetic treatment?

Recommendation (Grade A): corticosteroid is an effective antiemetic at recommended doses determined...
According to the emetic risk categories of chemotherapeutic regimens.

Corticosteroid has been used as an antiemetic prophylactic during cancer chemotherapy for 25 years [12], although its mechanism of action remains unclear compared with those of 5HT3 and NK1 antagonists, which have recently been approved with clear evidence of mechanisms. Although several classes of corticosteroid are available, dexamethasone and methylprednisolone are most frequently used as antiemetics, with strong evidence of their mechanisms. Although several classes of corticosteroid are available, dexamethasone and methylprednisolone are most frequently used as antiemetics, with strong evidence of their effects [13, 14]. In particular, oral and intravenous dexamethasone (4–20 mg/day) has been approved as antiemetic treatment during cancer chemotherapy in Japan. However, the efficacy of high-dose dexamethasone has not been compared with that of 20-mg treatments among either Western [13, 14] or Japanese populations [15].

CQ8. How should breakthrough nausea and vomiting be managed?

Recommendation (Grade B): fixed around-the-clock administration of a variety of drugs should be considered according to patient symptoms. In addition, antiemetic 5HT3 receptor antagonists should be replaced with another type of 5HT3 receptor antagonist.

Breakthrough emesis refers to nausea and vomiting despite prophylactic antiemetic treatment, and requires additional treatment with antiemetic agents with mechanisms of action that differ from that of the primary antiemetic agent. Among these, the dopamine antagonists metoclopramide, butyrophenone, corticosteroid, and lorazepam may be considered for breakthrough emesis, despite poor evidence of their efficacy. A systematic review of antiemetic treatments for patients with advanced cancer showed that metoclopramide is superior to placebo and equivalent to ondansetron, although responses were only 23–36 % and 18–52 % for nausea and vomiting, respectively [16]. Moreover, a randomized clinical controlled study of 51 advanced cancer patients showed no significant effects of additional dexamethasone for nausea after failure of antiemetic response to metoclopramide [17].

Some reports recommend antiemetic prophylaxis using agents that are not 5HT3 receptor antagonists.

CQ9. How should acute nausea and vomiting induced by low and minimum emetic chemotherapy be managed?

Recommendation (Grade B): during low emetic chemotherapy, dexamethasone should be considered according to chemotherapeutic regimen and patient background.

Recommendation (Grade C1): routine usage of dexamethasone is not recommended for minimum emetic chemotherapy.

Prophylactic antiemetic treatment is not recommended for low or minimum emetic chemotherapy, because patients do not progress to definite nausea and vomiting. Nonetheless, some patients suffer from emesis during treatment with low or minimum emetic chemotherapy, necessitating flexible and appropriate treatment despite the absence of high-level evidence. The 2006 ASCO and 2008 MASCC guidelines recommended administration of 4–8 mg dexamethasone [13, 18], and include prochlorperazine [19] and metoclopramide as optional antiemetics.

CQ10. How is nausea and vomiting managed for such regimens as several cisplatin treatments daily?

Recommendation (Grade B): a triple antiemetic regimen of 5HT3 antagonist, dexamethasone, and aprepitant is recommended for acute nausea and vomiting during more typical chemotherapeutic regimens. A double regimen of dexamethasone and aprepitant is recommended for delayed nausea and vomiting, even during regimens of several cisplatin treatments daily.

It is widely accepted that cisplatin is a highly emetic chemotherapeutic agent, and it is commonly administered every 3 or 4 weeks at >50 mg/m2 for treatment of a variety of malignancies. However, different cisplatin regimens have been established with reasonable evidence, including several cisplatin treatments daily at <50 mg/m2 for oncologic tumors such as cholangiocarcinomas, bladder cancers, and germinomas [20, 21], and continuous cisplatin injections at 100 mg/m2 over 4 days for non-Hodgkin malignant lymphomas.

CQ11. How should anticipatory nausea and vomiting be managed?

Recommendation (Grade B): initially, complete prevention of emesis is essential during acute and delayed phases, so patients never experience nausea and vomiting.

Recommendation (Grade B): benzodiazepine is effective for anticipatory nausea and vomiting.

Recommendation (Grade B): such psychological therapy as systematic desensitization and/or behavioral treatment, relaxation therapy, and hypnotherapy for pediatric patients effectively ameliorate anticipatory nausea and vomiting.

Anticipatory nausea and vomiting occurs immediately before treatment, and reflects previous negative experiences of cancer chemotherapy [22–24], although nausea is more common than vomiting among such cases. The ideal prophylaxis for this symptom is complete prevention of emesis from the initial treatment [23–26]. Hence, appropriate antiemetic treatments are essential, and require accurate assessment of emetic risks for planned chemotherapeutic regimens. The 2009 NCCN and 2008 MASCC guidelines recommended treatments with lorazepam [27] for anticipatory nausea and vomiting, and alprazolam [28] for anticipatory nausea.

CQ12. How are emetic risks categorized for radiation therapy?

Recommendation (Grade A): emetic risks of radiation therapy are classified (Table 3) according to tissue targets and volumes for irradiation.
As for chemotherapy, antiemetic treatments for radiation therapy are critical for successful treatment. Accordingly, the 2004 MASCC and 2006 ASCO guidelines indicate the emetic risk categories for specific targeted tissues, and recommend prophylactic antiemetic regimens based on these risk classifications. The risk of radiation-induced nausea and vomiting is categorized according to the percentage of patients who experience emesis. Moreover, whole body and upper abdominal radiation therapy are likely to cause greater emesis, and the frequency of nausea and vomiting increases with larger total doses and target tissue volumes [29, 30].

CQ13. Do antiemetic treatments differ in equivalent regimens from those in standard regimens containing specific key agents?

Recommendation (Grade C1): the emetic risk should be assessed on the basis of the agent with the highest emetic risk, even for similar chemotherapeutic regimens that comprise several agents.

Most clinically used chemotherapeutic regimes include several drugs, although many variations of standard chemotherapeutic regimens containing similar key agents. Thus, it is important to assess the emetic risks of regimens according to the emetic risks of each agent in isolation.

CQ14. What clinical factors and patient backgrounds affect CINV?

Recommendation (Grade C1): treatment and patient factors affect the emetic risks of CINV. Treatment factors include emetogenicity and dosages of chemotherapeutic agents, and tissue targets and volumes of radiation therapy. Relevant patient factors include age, gender, and alcohol consumption.

The frequency and intensity of emesis from CINV are affected by numerous factors, including specific chemotherapeutic agents, regimens, dosages, schedules, routes of administration, and tissue targets and volumes for radiation therapy. In addition, patient factors such as age [31], gender [31, 32], alcohol consumption [33], and experience of nausea gravidarum affect the emetic effects of CINV. The NCCN guideline also suggests that bowel obstruction, vestibulopathy, brain metastasis, electrolyte dysboslim, uremia, opioid use, gastric atony, and mental disorders are potential risk factors for emesis. Accordingly, management of treatment-related emesis is well-established with consensus, whereas patient-oriented factors remain unclear.

CQ15. How should CINV be managed in pediatric patients with malignancies?

Recommendation (Grade C1): multidisciplinary management using 5HT3 receptor antagonists, corticosteroid, and other antiemetic agents control the emetic effects of CINV, even for pediatric patients.

In the last three decades, advances in cancer treatment, for example high dose methotrexate, etarabine, cyclophosphamide, and hematonic stem cell transplantation, have led to long term prognoses for ≥70% of pediatric patients with malignancies. However, there are only a few reports with high level evidence about antiemetic treatment in pediatric patients from western populations [34–36]. Accordingly, they are treated with modified dosage on the basis of results of clinical trials on adult patients. Proper antiemetic treatments also enable pediatric patients to receive cancer chemotherapy without decline in QOL.

CQ16. Is it possible to discriminate nausea from anorexia, pyrosis, and dyspepsia? Which diseases produce symptoms of nausea and vomiting?

Recommendation (Grade B): no definitive evidence distinguishes nausea from anorexia, pyrosis, and dyspepsia. However, proton pump inhibitors (PPI) and H2 blockers are recommended for patients with these symptoms.

Recommendation (Grade C1): antiemetic agents should be used on the basis of accurate assessment of patient conditions.

Symptoms of anorexia, pyrosis, and dyspepsia are caused by several factors related to digestive dysfunction, and are frequently accompanied with nausea and other symptoms. Therefore, nausea induced by chemotherapy has not been strictly distinguished from other symptoms of digestive dysfunction. Nonetheless, PPI and H2-blockers are recommended as optional treatments for these symptoms [37].

In addition to treatments for CINV, patients with malignancies may suffer from nausea and vomiting as a result of the following conditions:

- Partial or complete bowel obstruction
- Vestibulopathy

Table 3  Emetic risk category for radiation therapy

| JSCO emetic risk category | Treated area |
|--------------------------|-------------|
| High emetic risk (emetic frequency: >90 %) | Total body |
| Moderate emetic risk (emetic frequency: 30–90 %) | Upper abdomen |
| Low emetic risk (emetic frequency: 10–30 %) | Lower thorax |
| Minimum emetic risk (emetic frequency: <10 %) | Head and neck |
| | Pelvis |
| | Cranium (radiosurgery) |
| | Craniospinal |
| | Extremities |
| | Breast |
– Brain metastasis
– Electrolyte dysbolism (hypercalcemia, hyponatremia, and hyperglycemia)
– Uremia
– Other combinations of drugs, including opioids
– Gastric atony
– Anticipatory nausea and vomiting

CQ17. How are different forms of agents appropriately selected and used?

Recommendation (Grade B): patients should self-manage the use of oral agents. However, in circumstances in which nausea and vomiting prevent patients from taking oral treatments, optional intravenous administration should be considered.

Antiemetic agents are available in a variety of formulations for oral, rectal, intravenous, and intramuscular administration. A meta-analysis of randomized control trials showed equivalence of oral and intravenous 5HT3 receptor antagonists [38]. However, the cost effectiveness and convenience of administration of oral agents are superior to those of intravenous agents, particularly when administered as tablets that disintegrate orally. Nonetheless, intravenous agents may improve treatment adherence among pediatric patients.

CQ18. For which antiemetic drugs are pharmacokinetic interactions observed?

Recommendation (Grade B): it is essential that aprepitant is used carefully to avoid interactions with co-administered drugs, including some chemotherapeutic agents. Moreover, strict dose control of combined drug regimens according to patient conditions and disease backgrounds is critical.

Because aprepitant induces and inhibits the cytochrome P450 enzymes 3A4 (CYP3A4) and 2C9 (CYP2C9) it can alter plasma concentrations of co-administered drugs by interacting with these critical drug-metabolizing enzymes [39]. Chemotherapeutic agents that are metabolized by CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine. Although doses were not adjusted for several chemotherapeutic agents used concurrently with aprepitant in phase III trials, these drugs should be used with caution [40, 41] because aprepitant interacts with several non-chemotherapeutic drugs, including warfarin, dexamethasone, and methylprednisolone. Concurrent use of aprepitant temporarily reduces prothrombin time–international normalized ratio (PT–INR) for patients receiving regimens that contain warfarin, necessitating anticogulant monitoring for these patients [42]. Aprepitant also increases AUCs of the corticosteroids dexamethasone and methylprednisolone, necessitating appropriate reductions of corticosteroid doses (CQ7) [39]. However, to ensure anti-cancer effects, steroid doses should not be reduced in chemotherapeutic regimens for malignant lymphoma that include corticosteroid, despite concomitant use of aprepitant. Moreover, concurrent use of the CYP3A4 inhibitors ketoconazole, itraconazole, and erythromycin may increase aprepitant AUCs, whereas the CYP3A4 inducers carbamazepine, rifampicin, and phenytoin may reduce plasma levels of aprepitant.

CQ19. How are the effects of antiemetic treatment evaluated?

Recommendation (Grade A): the effects of antiemetic treatment should be assessed at every visit for outpatients, and within 24 h after administration of chemotherapy for admitted patients.

Recommendation (Grade C1): strict assessments require patients to report their conditions to medical staff by using self-reporting systems.

No definitive evidence or consensus has been published for assessment of antiemetic treatments. However, successful anticancer treatment depends on optimum patient assessments, and nausea and vomiting are observed for 31 and 20 % of cancer patients, respectively [43]. Accordingly, the 2009 NCCN guidelines for palliative care recommend optimum screening for supportive care of all oncology patients according to their symptoms throughout the entire clinical course. Moreover, the RAND Cancer Quality-Assessing Symptoms Side Effects and Indicators of Supportive Treat-ment Project recommends symptom evaluations for all cancer patients, at every outpatient visit, and within 24 h of hospital admission. The 2009 NCCN Clinical Practice Guidelines for Antiemetics in Oncology suggest that prevention of nausea and vomiting is a primary objective. Hence, prophylactic treatment is mandatory for ≥4 days, because the emetic risks of CINV continue for several days under conditions of highly or moderately emetogenic cancer chemotherapy [44]. Moreover, complete responses were reportedly not achieved for acute and delayed emesis, despite optimum prophylactic treatment [40].

Differential diagnosis of the causes of emesis are necessary during clinical evaluations (CQ14, 16). However, common terminology criteria for adverse events (CTCAE) may remain useful when chemotherapeutic regimens are applied, and are based on objective assessments by medical staff rather than subjective assessments by patients. Nonetheless, applicable patient directed subjective evaluations include the numerical rating scale (NRS), the visual analog scale (VAS), the verbal rating scale (VRS) and the Wong–Baker face rating scale. In addition, index of nausea, vomiting and retching (INVIR) [44], Morrow assessment of nausea and emesis (MANE) [45], and functional living index-emesis (FLIE) scores [46] are also applicable as tools for evaluating longitudinal changes in emesis and the ensuing effects on quality of life.
ally relieved within a few days of opioid administration. Nonetheless, opioid-induced emesis is usu-
tant for successful pain control among cancer patients.

antiemetic treatments for opioid-induced emesis are impor-
and vomiting on initiation of opioid therapy. However, endoscopic stents are recom-
manded to resolve symptoms of simple intestinal obstruction for patients with poor prognosis.

Bowel obstruction among patients with advanced meta-
static disease reduces quality of life and causes difficulty
in the continuation of anticancer treatments. Conserva-
tive treatments are usually used for such patients, because
of poor prognosis as a result of advanced oncological sta-
tus. However, 50 % of colon cancer patients and 6–34 %
of gynecologic cancer patients suffer from benign bowel
obstructions [47], so accurate diagnoses is required.

CQ21. How are opioid-induced nausea and vomiting managed?

Recommendation (Grade B): emesis that is induced by
opioid use should be managed by use of antiemetic treat-
ments, although opioid rotation or changes in routes of
administration may be considered.

Recommendation (Grade C1): prophylactic antiemetic
treatments during opioid therapy may be useful despite the
lack of high-level evidence of efficacy and safety.

The WHO ladder strongly recommends opioid use for
oncological pain and cites high-level evidence of efficacy
and safety. Moreover, three opioid receptors, the δ and κ
receptors for emetogenic functions and the μ receptor for
antiemetic functions, have been characterized. Patients
frequently suffer from constipation, sleepiness, nausea,
and vomiting on initiation of opioid therapy. However,
antiemetic treatments for opioid-induced emesis are im-
portant for successful pain control among cancer patients.
Moreover, differential diagnosis of other causes is im-
portant in patients suffering from emesis after opioid treat-
ments (CQ16). Nonetheless, opioid-induced emesis is usu-
ally relieved within a few days of opioid administration.

Discussion

The purpose of these practice guidelines is to disseminate
treatment recommendations for daily practice according
to CQ relating to medications. Thus, 21 CQ pertaining to
antiemetic therapy, including prophylactic and retrospec-
tive antiemetic treatments, were generated. In this literature
review, most of the evidence was collected from foreign
studies reporting high-level evidence that was acceptable
for Japanese cancer patients. Therefore, these recommenda-
tions for standard therapy, depending on the grade of rec-
ommendation, were made on the basis of systematic review
and meta-analysis of antiemetic therapy. Consequently, the
CQs and their recommendations were similar to those pub-
lished in previous guidelines that have been used globally.
However, most reported evidence fails to consider ethnicity
and Japanese health-care systems. Thus, after release of the
guidelines, their penetration and dissemination to Japanese
medical practitioners was evaluated. To this end, current use
of antiemetic treatment in Japan was analyzed on the basis
of data obtained from a nationwide questionnaire. Response
was 88 % and use of the guidelines 78 % (in press).

Conclusion

In this manuscript we present, in English, of the 2010 JSCO
clinical practice guidelines for antiemesis. High concord-
ance with other antiemetic guidelines reflected their evi-
dence-based nature. After release of these guidelines, high
recognition and penetration was achieved for antiemetic
medicine in Japan, thus contributing to effective antiemetic
therapy for Japanese patients with malignancies.

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