

# Clinical Guideline for Pharmacological Management of Cancer Pain: The Japanese Society of Palliative Medicine Recommendations

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Pain is the most frequent and distressing symptom in cancer patients. As part of a worldwide effort to improve the quality of pain control, several clinical guidelines for the management of cancer pain have been published and revised in the last decade. The Japanese Society of Palliative Medicine first published a Japanese clinical guideline for the management of cancer pain in 2000. Since then, many clinical studies concerning cancer pain management have been conducted, new drugs have become available in Japan and the methodology of developing a guideline has been refined. Therefore, we decided to develop a novel clinical guideline. This review paper summarizes the recommendations and the rationales of this new clinical guideline for the pharmacological management of cancer pain. In addition, a short summary of the clinical guideline development process is provided. This new Japanese Society of Palliative Medicine guideline highlights the importance of conducting well-designed studies to identify the best practices in cancer pain management.

*Key words: cancer pain – opioid analgesics – nonopioid analgesics – guideline*

## INTRODUCTION

Pain is the most distressing symptom in cancer patients, and it affects 70–80% of patients with advanced disease (1). Current evidence from countries including Japan suggests that many cancer patients suffer from pain and do not receive adequate pain relief (2–7). As part of a worldwide effort to improve the quality of pain control, several clinical guidelines for the management of cancer pain have been published and revised in the last decade (8–13). As one of such efforts, the Japanese Society of Palliative Medicine (JSPM) first published a Japanese clinical guideline for the management of cancer pain in 2000 (14). Although a formal systematic review was conducted, recommendations of the JSPM guideline in 2000 were the same as the existing guidelines and the grading system of recommendations was anecdotal. Since then, many

clinical studies concerning cancer pain management have been conducted, and new drugs have become available in Japan. In addition, the methodology of developing a guideline has been refined (15,16). A novel clinical guideline to integrate new findings using the validated methodology is warranted.

This review paper summarizes the recommendations and the rationales for this new clinical guideline for the pharmacological management of cancer pain. In addition, a short summary of the development process for this guideline is provided.

## SHORT SUMMARY OF THE DEVELOPMENT PROCESS

The objective of developing the guideline was to establish the standard pharmacological management of cancer pain. The

target population includes all cancer patients who experience pain, whereas the primary users of this guideline are all medical personnel who care for cancer patients, including palliative care physicians, oncologists, nurses and pharmacists.

#### TASK FORCE

The committee of JSPM nominated the task force members from a pool of specialists with adequate clinical experience to cover multidisciplinary areas, and the JSPM Board gave the final approval. The task force comprised 56 physicians (31 palliative care physicians, 15 anesthesiologists, 5 oncologists and 5 home care physicians), 25 pharmacists, 23 nurses, 1 epidemiologist and 7 other professionals (Appendix).

#### SYSTEMATIC LITERATURE REVIEW

First, the task force gathered clinical questions by administering a questionnaire to all members of the task force. These items were then restructured into 65 questions. Next, the task force performed a systematic literature review of each clinical question using the electronic search function in the PubMed database; a manual search of all articles published in the *Journal of Pain and Symptom Management* and *Palliative Medicine* from January 2000 to July 2008, a search of the PaPaS (Pain, Palliative and Supportive Care) category of the Cochrane database and a review of reference literature of relevant guidelines (8–13) and textbooks (17–22). This review process included only studies that evaluated drugs available in Japan. The abstracts of all identified literature references were read, and the full text of all relevant literature was reviewed.

#### DRAFTING RECOMMENDATIONS AND DELPHI METHODS

Each member in charge of a clinical question drafted the recommendations and general background descriptions. The Delphi method was then performed to examine the validity of each statement. The Delphi method is a standardized method

used to reach consensus; we used the modified Delphi method (23). All statements in the clinical guideline were separated into >150 meaningful units, and the task force members were requested to rate the validity of all statements on a nine-point Likert-type scale from one (inappropriate) to nine (appropriate). After three Delphi rounds and an external review by 12 external reviewers (5 palliative care physicians, 2 radiation oncologists, 1 anesthesiologist, 1 home care physician, 1 nurse, 1 pharmacist and 1 epidemiologist), the final version was established.

#### EVIDENCE AND RECOMMENDATION LEVELS

The task force decided to use an original recommendation table for this clinical guideline, following the concepts from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to articulate the levels of evidence and the strengths of each recommendation (Table 1) (15). We decided to use ‘should’ for expressing recommendation strength 1 and ‘may’ for recommendation strength 2 in this paper.

#### RECOMMENDATIONS

We created 65 recommendations: 24 for the general management of cancer pain, 24 for the management of pain from specific etiologies, 15 for the management of opioid-induced adverse effects and 2 for patient education. This guideline also included chapters on general background descriptions, flow charts to visualize the recommendations, a complete reference list followed by the search strategy and a summary of other related international guidelines that have previously been published.

Table 2 demonstrates all the recommendations listed in the guideline, and Fig. 1 shows an overview and the main algorithm for using those recommendations.

The key recommendations and their rationales are described below.

**Table 1.** Recommendation table

Strength of recommendation	
1 (strong)	Recommended treatment is certainly of benefit to the patient, and the benefit exceeds the harm or burden. In the statement, ‘should’ is used.
2 (weak)	Recommended treatment may be of benefit to the patient. Or the benefit competes with the harm or burden from the recommended treatment. In the statement, ‘may’ is used.
Level of evidence	
A (high)	The evidence from the results of studies is established. The result will not change, even if further study is performed, e.g. multiple high-quality randomized controlled trials with concordant results, or a meta-analysis of randomized controlled trials
B (low)	Although some studies support the result, evidence is not enough. Further study may change the result, e.g. randomized, controlled trials with inconsistent results, low-quality randomized controlled trials, small number of randomized controlled trials, non-randomized controlled trials or multiple observational trials with consistent results
C (very low)	There is insufficient evidence for the result, e.g. small number of observational trials, case reports and expert opinions

**Table 2.** Recommendations in the guideline of the Japanese Society of Palliative Medicine**1. Management of cancer pain***1.1 Assessment*

- 1.1.1 Comprehensive assessment of pain should be carried out.

*1.2 Patients with mild pain*

- 1.2.1 Acetaminophen should be administered to cancer patients with mild pain [1A].
- 1.2.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) should be administered to cancer patients with mild pain [1B].
- 1.2.3 The type of non-opioid analgesic should be chosen in accordance with the effectiveness and tolerability of an individual patient [1A].
- 1.2.4 Prostaglandin E1 analogs, proton pump inhibitors or H2 receptor blockers should be used for the prevention of peptic ulcer in patients who are treated with an NSAID [1A].

*1.3 Patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics*

- 1.3.1 Opioids should be administered to cancer patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics [1B].
- 1.3.2 The type of opioid should be chosen individually according to the patient's condition [1B].
- 1.3.3 In cancer patients with stable and mild-to-moderate pain, either sustained-release or immediate-release opioids may be used. In cancer patients with severe or unstable pain, immediate-release opioids or parenteral opioids may be used [2B].
- 1.3.4 Patients should be carefully assessed and observed for nausea/vomiting during opioid therapy, and antiemetics should be readily available whenever nausea/vomiting occurs [1C].
- 1.3.5 Patients should be carefully assessed and observed for constipation during opioid therapy; moreover, they should be provided with instructions regarding adequate fluid intake, diet and laxatives for the prevention of constipation [1C].
- 1.3.6 Nonopioid analgesics may be continued when opioids are introduced in patients with inadequate pain control by nonopioid analgesics [2B].

*1.4 Patients with inadequately controlled pain despite initial opioid use*

- 1.4.1 Non-opioid analgesics should be used concurrently with opioids in patients who experience continuous pain with regular opioid use [1A].
- 1.4.2 The dose of regular opioid should be increased in patients who experience continuous pain with regular opioid use [1B].
- 1.4.3 Type of opioid should be switched in patients with inadequately controlled pain under a certain type of opioids [1B].
- 1.4.4 Another type of opioid may be added in patients with inadequate pain control by a certain type of opioid [2C].
- 1.4.5 The administration route may be changed to intravenous or subcutaneous infusion in patients with inadequate pain control with an oral or a transdermal preparation of opioid analgesics [2C].
- 1.4.6 Ketamine may be used in combination with opioids in patients with inadequately controlled pain after a sufficient increase in opioid dose [2B].
- 1.4.7 Corticosteroids may be used in combination with opioids only for particular pain etiologies, paying careful attention to the risk of adverse reactions in patients who experience pain after a sufficient increase in opioid dose [2C].

*1.5 Patients with breakthrough pain*

- 1.5.1 The rescue dose of opioids should be used in patients with breakthrough pain [1B].
- 1.5.2 The rescue dose may be increased if adverse events are acceptable and the initial rescue dose provides inadequate analgesic effects [2C].
- 1.5.3 For patients with end-of-dose failure, the dose of regular opioids should be increased or interval of regular opioids should be shortened [1B].

**2. Treatment of pain from specific etiology***2.1 Neuropathic cancer pain*

- 2.1.1 Any of the adjuvant analgesics (anticonvulsants, antidepressants, antiarrhythmics, ketamines or corticosteroids) may be used in cancer patients with neuropathic pain [2B].
- 2.1.2 Another type of adjuvant analgesics may be added in patients with inadequate control of neuropathic pain after increasing the dose of a certain adjuvant analgesic sufficiently, in consultation with an expert [2C].

*2.2 Bone metastatic pain*

- 2.2.1 Bisphosphonate may be used in patients with pain from bone metastasis, in consideration of expected prognosis [2B].

*2.3 Epigastric pain due to pancreatic cancer*

- 2.3.1 Celiac plexus block may be performed in patients with epigastric pain due to pancreas cancer [2A].

*2.4 Pain in the thoracic area*

- 2.4.1 Nerve block (such as epidural block, intercostals nerve block, nerve root block or intrathecal phenol block) may be performed in patients with pain in the thoracic area [2C].

*Continued*

Table 2. Continued

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- 2.5 Perineal pain
- 2.5.1 Saddle block or superior hypogastric plexus block may be performed in patients with perineal pain [2C].
- 2.6 Pain from malignant psoas syndrome
- 2.6.1 Muscle relaxants may be used in patients with malignant psoas syndrome [2C].
- 2.6.2 Nerve block (such as epidural block or nerve root block) may be performed in patients with malignant psoas syndrome [2C].
- 2.7 Pain from malignant bowel obstruction
- 2.7.1 Octreotide or scopolamine butylbromide may be used in patients with pain from malignant bowel obstruction [2B].
- 2.7.2 Corticosteroids may be used in patients with pain from malignant bowel obstruction [2B].
3. Treatment of adverse events of opioids
- 3.1 Nausea/vomiting
- 3.1.1 Etiology of nausea/vomiting should be assessed, and any reversible etiology should be treated.
- 3.1.2 Anti-emetics should be used in patients developing nausea/vomiting on opioids. Type of anti-emetics should be chosen from anti-dopaminegics, prokinetics, or antihistaminics [1C].
- 3.1.3 Type of opioids should be switched to another in patients developing nausea/vomiting on a certain opioid [1B].
- 3.1.4 Administration route may be changed to intravenous or subcutaneous infusion in patients developing nausea/vomiting on oral opioids [2C].
- 3.2 Constipation
- 3.2.1 Etiology of constipation should be assessed, and any reversible etiology, especially fecal impaction or bowel obstruction, should be treated.
- 3.2.2 Laxatives should be used in patients developing constipation on opioids [1B].
- 3.2.3 Type of opioids should be switched to fentanyl in patients on morphine or oxycodone with refractory constipation after laxatives [1B].
- 3.3 Drowsiness
- 3.3.1 Etiology of drowsiness should be assessed, and any reversible etiology should be treated. The possibility of opioid overdose should also be assessed.
- 3.3.2 Psycho-stimulants may be used in patients developing drowsiness on opioids, in consultation with an expert [2C].
- 3.3.3 Type of opioids should be switched to another in patients with drowsiness on a certain opioid [1B].
- 3.3.4 Administration route may be changed to intravenous or subcutaneous infusion in patients developing drowsiness on oral opioids [2C].
- 3.4 Delirium
- 3.4.1 Etiology of delirium should be assessed, and any reversible etiology should be treated.
- 3.4.2 Anti-psychotics may be used in patients developing delirium on opioids [2B].
- 3.4.3 Type of opioids should be switched to another in patients with delirium on a certain opioid [1B].
- 3.4.4 Administration route may be changed to intravenous or subcutaneous infusion in patients developing delirium on oral opioids [2C].
4. Patient education in cancer pain management
- 4.1.1 Patients should be given education about cancer pain management [1A].
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JSPM, Japanese Society of Palliative Medicine

## ASSESSMENT OF CANCER PAIN

- (i) A comprehensive assessment of the pain should be performed. A comprehensive assessment includes an assessment of the etiology of the pain and that of the pain itself.

The influence of the pain on daily life; the pattern, intensity, location and quality of pain; and the exacerbating/relieving factors should be evaluated. In addition, the response to current treatment and the effectiveness of a rescue dose should be evaluated.

For assessing the etiology of cancer-related pain, it is important to evaluate whether it is directly related to the cancer itself and/or to its treatment. In addition, it is important to evaluate whether the pain is a sign of an oncological

emergency and identify its etiology (e.g. neuropathic pain, bone pain and perineal pain). This assessment includes history, physical examinations and imaging studies, and it must lead to a therapeutic approach.

## PATIENTS WITH MILD PAIN

- (i) Acetaminophen should be administered to cancer patients with mild pain. [1A]

A randomized controlled trial of patients with advanced cancer demonstrated that acetaminophen decreased pain intensity to a significantly greater extent than placebo (24). A Cochrane review also concluded that acetaminophen is more effective than placebo in improving cancer pain (25).

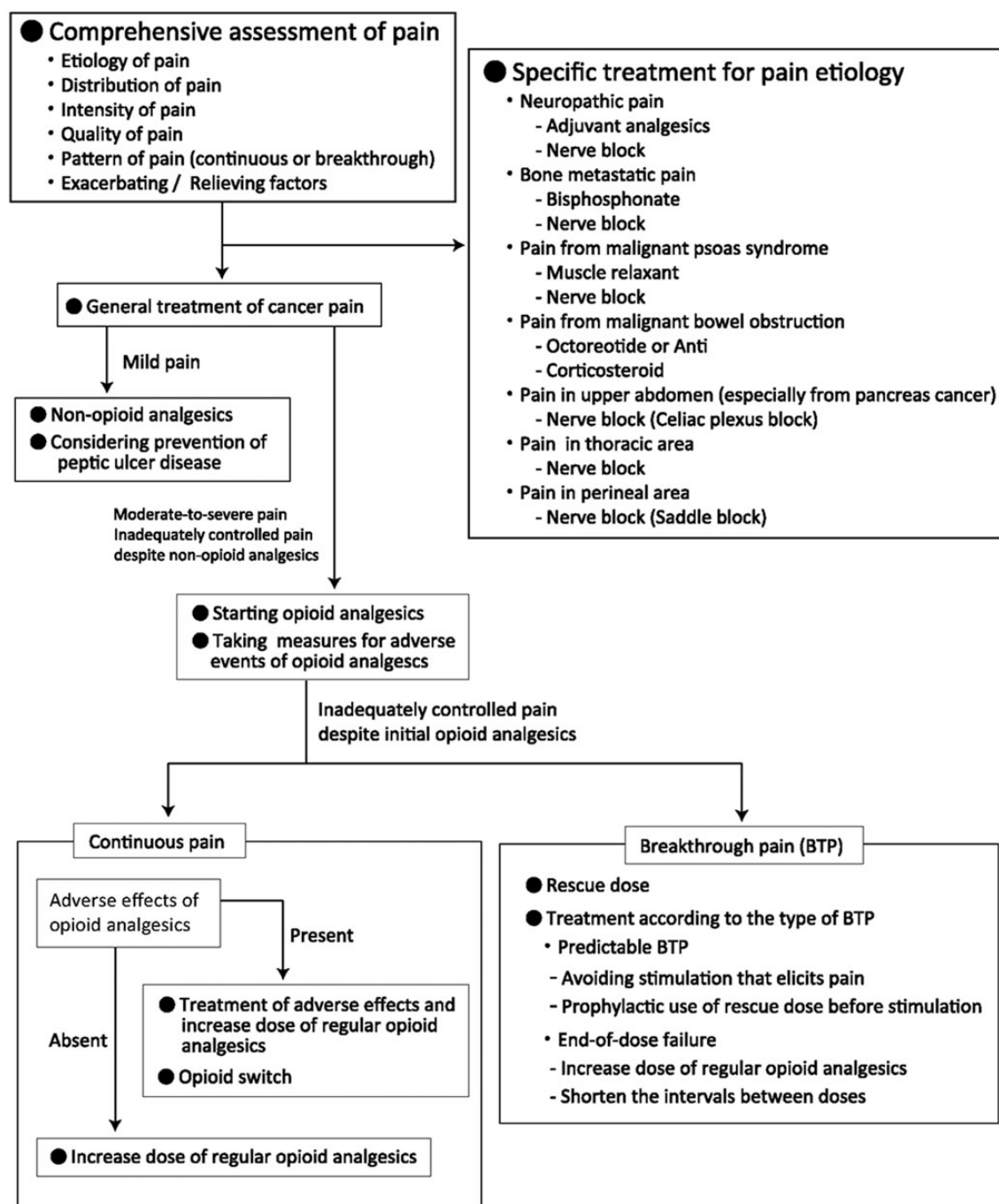


Figure 1. Overview of recommendations.

Because the available evidence shows that acetaminophen decreases pain in cancer patients who are not prescribed any analgesics, the panel has agreed that acetaminophen should be administered to cancer patients with mild pain.

- (ii) Non-steroidal anti-inflammatory drugs should be administered to cancer patients with mild pain. [1B]

Several small, randomized controlled trials demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs)

decreased pain intensity in cancer patients to a significantly greater extent than placebo (26–28). A recent systematic review, including seven randomized controlled trials, concluded that NSAIDs are more effective than placebo in improving cancer pain (25).

Because the available evidence demonstrates that NSAIDs decrease pain in cancer patients who are not prescribed any analgesics, the panel has agreed that NSAIDs should be administered to cancer patients with mild pain.



- (iii) The nonopioid analgesic type should be chosen in accordance with the effectiveness and tolerability of an individual patient. [1A]

Several small studies comparing different nonopioid analgesics demonstrated no significant difference in the effectiveness in treating cancer pain and the incidence of adverse events (29–32). A systematic review concluded that there is no evidence of the superiority of certain nonopioid analgesics over others (25).

Because the available evidence shows no superiority of certain nonopioid analgesics over others in terms of either efficacy or adverse event profile, the panel has agreed that the type of nonopioid analgesic should be chosen in accordance with the effectiveness and tolerability of an individual patient (e.g. renal function, risk of peptic ulcer, and bleeding tendency).

- (iv) Prostaglandin E1 analogs, proton pump inhibitors, or H2 receptor blockers should be used for the prevention of peptic ulcer in patients who are treated with an NSAID. [1A]

According to the Evidence-Based Guideline for Gastric Ulcer in Japan (33), the efficacy of prostaglandin E1 analogs, proton pump inhibitors and high-dose H2 receptor blockers for the prophylaxis of NSAID-induced peptic ulcer has been demonstrated in several randomized controlled trials and systematic reviews.

Therefore, prostaglandin E1 analogs, proton pump inhibitors, or H2 receptor blockers should be used for the prevention of peptic ulcer in patients who are treated with an NSAID.

#### PATIENTS WITH MODERATE-TO-SEVERE PAIN OR INADEQUATELY CONTROLLED PAIN DESPITE TREATMENT WITH NONOPIOID ANALGESICS

- (i) Opioids should be administered to cancer patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics. [1B]

For patients with moderate-to-severe pain or inadequate pain control with a nonopioid analgesic, the World Health Organization (WHO) guideline recommends the use of Step 2 opioids first, and switching to Step 3 opioids (3-step strategy) afterward. Several observational studies have revealed the efficacy of this WHO analgesic ladder (34,35). Therefore, using the three-step strategy is likely to be safe and effective.

On the other hand, two randomized controlled trials demonstrated that using a Step 3 opioid first (two-step strategy) is significantly more effective than using the three-step strategy, in improving cancer pain (36,37). However, some adverse events such as nausea or constipation tended to be more frequent in the two-step strategy group in these studies.

Available evidence suggests that the three-step strategy is effective without troublesome adverse events, and the two-step strategy is more effective than the three-step strategy, but with more adverse events. Therefore, opioids should

be administered to cancer patients with moderate-to-severe pain or inadequately controlled pain despite treatment with nonopioid analgesics, using both the three-step and two-step strategies.

- (ii) The type of opioid should be chosen individually according to the patient's condition (i.e. availability of administration route, medical complications, coexisting symptoms and pain intensity). [1B]

A Cochrane review including 54 randomized controlled trials concluded that morphine is effective in improving cancer pain (38).

The efficacy of using oxycodone was evaluated in an observational trial including 390 cancer patients with moderate-to-severe pain (39). In this trial, the intensity of pain was significantly decreased after the administration of oxycodone, and there were no serious adverse events. A systematic review of four studies comparing oxycodone and morphine concluded that oxycodone is as effective as morphine in improving cancer pain (40). Also, a recent, small, randomized, controlled trial comparing the effectiveness of sustained-release oxycodone with that of sustained-release morphine in improving cancer pain demonstrated that these two preparations exerted an approximately equivalent analgesic effect (41).

Four randomized controlled trials comparing the efficacy of morphine with that of transdermal or intravenous fentanyl demonstrated no significant difference in analgesic effect between the groups (42–45). Two of these four studies demonstrated that the incidence of constipation was significantly lower in the fentanyl group than in the morphine group. Among the empirical studies using transdermal fentanyl as the initial opioid, two observational studies demonstrated that the intensity of pain decreased in a majority of patients, without the presence of serious adverse events (46,47). A randomized controlled trial comparing the efficacy of transdermal fentanyl with that of sustained-release morphine as the initial opioid in patients with mild-to-moderate pain demonstrated no significant difference in analgesic effect between the groups in the transdermal fentanyl group (48).

Available evidence showed no significant differences between morphine, oxycodone and fentanyl, regarding the efficacy. Therefore, the type of opioids should be chosen individually according to the patient's condition.

The administration route chosen should be the one most convenient and preferable to the patient. In general, the oral route is preferred. In case of difficulty in using the oral route, continuous parenteral infusion or transdermal or rectal routes can be chosen according to patient's preference.

Regarding complications, morphine is best avoided in patients with renal insufficiency because accumulation of active metabolites can lead to adverse events (49). Regarding coexisting symptoms, fentanyl causes constipation less frequently than other opioids (44,45,48); therefore, fentanyl is preferable in patients with severe constipation or those who need to avoid a decrease in bowel movements. Morphine has

been demonstrated to be effective in alleviating dyspnea in cancer patients (50); therefore, morphine is preferable in patients with dyspnea.

Regarding pain intensity, adjusting the dose of transdermal fentanyl within short time intervals is difficult because of its long half-life. Therefore, transdermal fentanyl should not be used as the initial opioid in patients with severe or unstable pain.

- (iii) In cancer patients with stable and mild-to-moderate pain, either sustained-release or immediate-release opioids may be used. In cancer patients with severe or unstable pain, immediate-release opioids or parenteral opioids may be used. [2B]

A Cochrane review analyzed 15 randomized controlled trials that compared the efficacy of immediate-release and sustained-release morphine, and concluded that these two formulations are equivalent in terms of analgesic effect and incidence of adverse events, when used as around-the-clock opioids (38). The same result has been demonstrated in a double-blind, randomized controlled trial comparing immediate- and sustained-release oxycodone (51).

Although available evidence suggests that either immediate-release or sustained-release opioids can be used as around-the-clock opioids, patients with severe or unstable pain were excluded from these studies. The panel has agreed that either immediate-release or sustained-release opioids may be used as around-the-clock opioids in patients with mild-to-moderate stable pain, and a rapid titration with immediate-release opioids or parenteral opioids is desirable in patients with severe or unstable pain.

- (iv) Patients should be carefully assessed and observed for nausea/vomiting during opioid therapy and antiemetics should be readily available whenever nausea/vomiting occurs. [1C]

Because there are, to date, no clinical trials evaluating the efficacy of prophylactic antiemetics against opioid-induced nausea/vomiting, current evidence of prophylactic antiemetic use remains insufficient.

On the basis of panel consensus, this guideline recommends that patients should be observed carefully for the development of nausea/vomiting during opioid therapy, and that antiemetics should be prescribed as required when nausea/vomiting occurs. Once opioid-induced nausea/vomiting develops, antiemetics should be continued for 1 to 2 weeks because tolerance to opioid-induced nausea/vomiting may develop within 1 to 2 weeks after initiating opioid therapy.

The type of antiemetic can be chosen from dopamine antagonists (e.g. haloperidol, prochlorperazine), gastrointestinal prokinetic agents (e.g. metoclopramide) or antihistamine drugs.

- (v) Patients should be carefully assessed and observed for constipation during opioid therapy; moreover, they should be provided with instructions regarding adequate

fluid intake, diet and laxatives for the prevention of constipation. [1C]

To date, there have been no clinical trials evaluating the efficacy of prophylactic laxative use for opioid-induced constipation. Despite insufficient evidence, on the basis of the panel consensus, this guideline recommends that patients should be carefully assessed and observed for constipation during opioid therapy, and that they should be provided with instructions regarding adequate fluid intake, diet, and laxatives as preventive measures against constipation, considering its high prevalence with chronic opioid therapy.

- (vi) Nonopioid analgesics may be continued when opioids are introduced in patients with inadequate pain control by nonopioid analgesics. [2B]

A double-blind, randomized controlled trial demonstrated that the addition of ibuprofen to oxycodone/acetaminophen therapy provided significantly better analgesic effects compared with placebo in cancer patients with pain from bone metastasis (52). In addition, another small, double-blind, crossover, randomized controlled trial demonstrated that the addition of a diclofenac suppository to regular parenteral morphine therapy provided significantly better analgesic effects than placebo in cancer patients (53). Furthermore, another open-label, randomized controlled trial demonstrated that the addition of oral ketorolac to regular morphine therapy showed an insignificant but better analgesic effect compared with morphine only (54). In this trial, dose escalation of morphine was significantly slower, whereas the maximum morphine dose was significantly lower in the ketorolac group. Ketorolac use tended to decrease opioid-related constipation but increased gastric discomfort. Another small, randomized controlled trial demonstrated that compared with the addition of placebo, the addition of acetaminophen showed a small but significantly better analgesic effect in cancer patients administered opioids (55).

Available evidence suggests that the use of a nonopioid analgesic combined with an opioid is more effective than using an opioid alone, despite the possibility of increasing incidence of gastric discomfort. We have therefore concluded that in patients with inadequately controlled pain despite treatment with nonopioid analgesics, nonopioid analgesics may be continued when opioids are introduced.

#### PATIENTS WITH INADEQUATELY CONTROLLED PAIN DESPITE INITIAL OPIOID USE

- (i) Nonopioid analgesics should be used concurrently with opioids in patients who experience continuous pain with regular opioid use. [1A]

As previously mentioned, four randomized controlled trials comparing the combined use of nonopioid analgesics and opioids with the use of opioids alone demonstrated the superiority of the combination in producing an analgesic effect (52–55).

Available evidence shows that the addition of a nonopioid analgesic decreases residual continuous pain in patients receiving only a regular opioid. However, because the analgesic effect of nonopioid analgesics is at most moderate and their long-term use may result in several adverse events, the decision of adding nonopioid analgesics to regular opioid therapy should be made after carefully weighing the benefits of the analgesic effect against the risk of adverse events.

- (ii) The dose of regular opioids should be increased in patients who experience continuous pain with regular opioid use. [1B]

Although to date, no clinical trials have compared the amount of increase in regular opioid dose and the interval between increments, several observational studies have demonstrated that the increase strategy based on the WHO method for cancer pain relief provided adequate pain relief (34,35).

Therefore, available evidence suggests that increasing the dose of regular opioids provides pain relief in patients with residual continuous pain despite regular opioid use. When increasing the dose of regular opioids, an increase of 30–50% of the regular daily dose is recommended. However, the total amount of rescue medication required on the previous day must be considered. With regard to the interval between doses, an interval of 24 h for immediate-release opioids or parenteral opioids, 48 h for sustained-release opioids and 72 h for transdermal fentanyl is recommended according to their expected time to achieve steady-state. In cases of severe pain that require prompt analgesia, parenteral opioids or immediate-release opioids are the desirable administration routes.

- (iii) The type of opioid should be switched in patients with inadequate pain control with a certain type of opioids. [1B]

A systematic review of 21 observational studies concluded that opioid switching was an effective measure to improve the balance between analgesia and adverse events as a whole (56,57). The studies included in this analysis mainly evaluated the switch from morphine to oxycodone or fentanyl.

Therefore, available evidence suggests that opioid switching could improve analgesic effects and decrease adverse events in cancer patients with inadequate pain control with a certain type of opioid.

- (iv) Another type of opioid may be added in patients with inadequate pain control with a certain type of opioid, after consultation with pain or palliative care specialists. [2C]

One observational study evaluating the effectiveness of opioid combination therapy in improving analgesic effects demonstrated that the addition of a second opioid decreased pain intensity without increasing adverse events in cancer patients with inadequate pain control after an increase in the dose of regular opioids (58).

Although the addition of another opioid may provide better analgesic effects in cancer patients with inadequately controlled pain, the present evidence is insufficient. In addition, the concurrent use of different types of opioids may affect compliance. The panel has concluded that after consultation with pain or palliative care specialists, another type of opioid may be added to patients with inadequate pain control with a certain type of opioid.

- (v) The administration route may be changed to intravenous or subcutaneous infusion in patients with inadequate pain control with an oral or a transdermal preparation of opioid analgesics. [2C]

Two observational studies evaluating the efficacy of changing to a continuous parenteral route demonstrated that this change decreased pain intensity, decreased adverse events and improved the quality of life in cancer patients with inadequate pain control with oral morphine or transdermal fentanyl (59,60).

Therefore, changing to a parenteral route may facilitate an improvement in the analgesic effect in cancer patients with inadequate pain control with oral or transdermal opioids.

- (vi) Ketamine may be used in combination with opioids in patients with inadequately controlled pain after a sufficient increase in opioid dose, after consultation with pain or palliative care specialists. [2B]

A systematic qualitative review including two randomized controlled trials to evaluate the efficacy of ketamine provided a modest conclusion that ketamine had a potential efficacy when used as an adjuvant to opioids for cancer pain (61).

Although the use of ketamine as an adjuvant to opioids may provide better analgesic effects in cancer patients with inadequately controlled pain after a sufficient increase in opioid dose, the present evidence is insufficient. In addition, using ketamine may increase central nervous system (CNS) side effects. The panel has concluded that, after consultation with pain or palliative care specialists, ketamine may be added in patients with inadequately controlled pain after a sufficient increase in opioid dose.

- (vii) Corticosteroids may be used in combination with opioids for particular pain etiologies, paying careful attention to the risk of adverse reactions in patients who experience pain after a sufficient increase in opioid dose. [2C]

A small, randomized controlled crossover trial demonstrated that pain intensity in patients with advanced cancer decreased after the administration of methylprednisolone with weak opioids (62). On the other hand, another randomized controlled trial demonstrated that, whereas dexamethasone provided a short-term benefit for gastrointestinal adverse events and improved a patient's sense of well-being, pain intensity was not significantly different between dexamethasone–opioid combination therapy and opioid monotherapy in cancer patients with moderate-to-severe pain (63).



Therefore, there is insufficient evidence for the efficacy of corticosteroids in combination with opioids. However, corticosteroids are considered to decrease the intensity of pain caused by a specific etiology such as spinal cord compression, inflammation, increased intracranial pressure and bone metastasis. Corticosteroids can be used in combination with opioids for pain caused by such etiologies if careful attention is paid to adverse events from long-term corticosteroid use (e.g. hyperglycemia, peptic ulcer, immune suppression, Cushing's syndrome, etc.). Corticosteroids should be continued at the minimum effective dose, and should be tapered and discontinued, when ineffective.

#### PATIENTS WITH BREAKTHROUGH PAIN

- (i) The rescue dose of opioids should be used in patients with breakthrough pain. [1B]
- (ii) The rescue dose may be increased if adverse events are acceptable and the initial rescue dose provide inadequate analgesic effects. [2C]

Although a Cochrane review on the management of breakthrough pain concluded that a rescue dose was effective for such pain, this systematic review primarily analyzed studies of oral transmucosal fentanyl citrate, which is not available in Japan (64). Although randomized placebo-controlled trials to evaluate the efficacy of oral and parenteral opioids are lacking, there are three observational studies evaluating the efficacy of a rescue dose of subcutaneous or intravenous opioids for breakthrough pain, and two randomized controlled trials of oral transmucosal fentanyl citrate that used oral and intravenous opioids as a control treatment (65–69).

A sub-analysis of a rescue dose of oral morphine in a randomized controlled trial demonstrated that immediate-release morphine caused a clinically significant decrease in breakthrough pain, and the mean intensity of pain decreased 60 min after administration (65). Two observational studies and a sub-analysis of a rescue dose of intravenous morphine in a randomized, controlled trial demonstrated that intravenous morphine caused a clinically significant improvement of breakthrough pain in a majority of patients (66–68). An observational trial demonstrated that subcutaneous morphine relieved breakthrough pain within 10 min in a majority of patients (69). In these studies, serious adverse events were rare.

Therefore, available evidence suggests that using a rescue dose ameliorates breakthrough pain in cancer patients receiving regular opioid doses.

The dosage used in current studies corresponded to 10–20% of the daily regular opioid dose, regardless of the administration route. These trial results suggest that this dose is safe and effective, and the panel has agreed that the starting dose of a rescue opioid should be 10–20% of the daily regular opioid dose when oral immediate-release opioids are used. On the other hand, for patients on continuous parenteral opioids, a 1 h bolus dose of regular parenteral opioid is traditionally

used in Japan; therefore, the panel has recommended the 1 h bolus administration in patients on continuous parenteral opioids.

A clinical trial showed that an adequate dose of the rescue opioid would not be completely correlated with the total daily dose of regular opioids (65). Therefore, the panel has agreed that the dosage of the rescue opioid should be increased and adjusted individually if adverse events are acceptable and the initial dose provides inadequate analgesic effects.

- (iii) For patients with 'end-of-dose failure,' the dose of regular opioids should be increased or the interval of regular opioid administration should be shortened [1B]

A small, randomized controlled trial comparing the effects of a dose of immediate-release morphine administered every 4 h with those of a bedtime double dose demonstrated that the pain intensity at night and the next morning as well as the requirement of a rescue opioid at night were significantly lower in the 4-h group (70). On the other hand, a small, randomized controlled trial comparing the same groups demonstrated that the pain intensity was not significantly different between the groups (71).

Although available evidence is insufficient to conclude whether an increase in the dose of regular opioids or shortening the dosing interval of regular opioids is appropriate to ameliorate 'end-of-dose failure,' the panel agreed that both the strategies can be used in cancer patients with 'end-of-dose failure' who are using regular immediate-release opioids.

There are no trials evaluating the efficacy of these 2 strategies in patients using regular sustained-release opioids. However, an increase in the dose of regular opioids presumably maintains effective blood concentration and improves 'end-of-dose failure' in patients using regular sustained-release opioids because of their prolonged duration of action. Therefore, the dose of regular opioids can be increased in cancer patients with 'end-of-dose failure' who are using regular sustained-release opioids. The dosing interval can be shortened when an increase in the dose of regular opioids is not effective or causes an adverse event.

#### NEUROPATHIC PAIN IN CANCER PATIENTS

- (i) Adjuvant analgesics (e.g. anticonvulsants, antidepressants, antiarrhythmics, *N*-methyl-D-aspartate (NMDA) receptor antagonist or corticosteroids) may be used in cancer patients with neuropathic pain. [2B]
- (a) Anticonvulsants

Two randomized, controlled trials evaluating the efficacy of gabapentin in cancer patients with neuropathic pain demonstrated that gabapentin as an adjuvant to opioids demonstrated a significantly better analgesic effect against neuropathic pain compared with placebo (72,73). Drowsiness was more frequent in the gabapentin group in both the studies. Also, in noncancer patients, a recent Cochrane systematic review concluded that gabapentin demonstrated a moderate analgesic

effect against neuropathic pain, with adverse effects such as dizziness, drowsiness and headache (74). Other than gabapentin, a randomized controlled trial comparing three arms (buprenorphine alone, phenytoin alone or buprenorphine and phenytoin) did not show any difference in analgesic effect among the three arms in cancer patients with neuropathic pain (75). A small, observational trial evaluating the efficacy of valproate as an adjuvant to opioids in cancer patients with neuropathic pain demonstrated that 56% patients exhibited a decrease in pain intensity (76). Another small, observational trial evaluating the efficacy of clonazepam as an adjuvant to opioids in cancer patients with neuropathic pain demonstrated that although the mean pain intensity decreased from three to one in five patients who completed the study protocol, another five patients dropped out because of worsening pain or drowsiness (77).

Therefore, available evidence suggests that gabapentin improves neuropathic pain in cancer patients. Although some other anticonvulsants may improve neuropathic pain in cancer patients, current evidence for the efficacy of these agents is insufficient.

#### (b) Antidepressants

A randomized controlled, crossover trial comparing the efficacy of amitriptyline, a tricyclic antidepressant (TCA), as an adjuvant to opioids with that of placebo in cancer patients with neuropathic pain showed that amitriptyline caused a small but significant improvement in maximum pain intensity (78). However, the incidence of adverse effects, such as drowsiness, confusion and dry mouth, was also significantly higher with amitriptyline. In noncancer patients, a recent Cochrane systematic review concluded that TCAs and venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), are effective for achieving at least moderate pain relief in patients with neuropathic pain (79).

Although available evidence is insufficient to establish the efficacy of antidepressants in cancer patients with neuropathic pain, on the basis of data from patients without cancer, TCAs and SNRIs can be used as an adjuvant to opioids in cancer patients with neuropathic pain.

#### (c) Antiarrhythmics

A randomized, controlled trial evaluating the efficacy of lidocaine (2 mg/kg by bolus infusion followed by a 2 mg/kg drip infusion for 1 h) for the treatment of opioid-refractory neuropathic and other types of pain in cancer patients demonstrated that lidocaine provided a significantly better analgesic effect compared with placebo, with minor adverse effects such as tinnitus and perioral numbness (80). In contrast, two small, randomized controlled, crossover trials evaluating the efficacy of lidocaine in cancer patients with neuropathic pain demonstrated no significant analgesic effect (81,82).

In noncancer patients, a recent Cochrane systematic review concluded that lidocaine and other oral analogs demonstrated better analgesic effects in cancer patients with neuropathic

pain compared with placebo, and were as effective as other analgesics (83).

Although the results of available evidence are conflicting and insufficient, the panel concluded that, on the basis of data from patients without cancer, antiarrhythmics may be used as adjuvants to opioids in cancer patients with neuropathic pain.

#### (d) NMDA receptor antagonists

A small, randomized, controlled, crossover trial evaluating the efficacy of ketamine against opioid-refractory neuropathic or mixed pain in cancer patients demonstrated that ketamine demonstrated a significantly better analgesic effect compared with placebo, with moderate adverse effects such as hallucination and sensation of insobriety (84). In two other small observational studies, ketamine demonstrated a clinically significant decrease in opioid-refractory neuropathic pain in 61–77% patients with cancer (85,86).

Although available evidence is insufficient and there is a well-documented risk of a CNS adverse effect, ketamine may be used as an adjuvant to opioids in cancer patients with opioid-refractory neuropathic pain.

#### (e) Corticosteroids

Although to date, no clinical trials have evaluated the efficacy of corticosteroids in the treatment of neuropathic pain in cancer patients, corticosteroids are considered to improve the intensity of pain caused by a specific etiology such as spinal cord compression, nerve compression or inflammation.

The panel agreed that corticosteroids can be used as an adjuvant to opioids for neuropathic pain caused by spinal cord compression, other nerve compression by tumor invasion or inflammation in the nervous system.

## DISCUSSION

We reported the summary of recommendations of a new Japanese clinical guideline for the management of cancer pain. Although we used a formal evidence-based methodology for constructing this clinical guideline, a majority of the recommendations are based on poor-quality controlled trials, observational studies or expert opinions. This finding confirms that a worldwide effort for conducting well-designed, controlled trials is essential for improving the clinical guideline and management of cancer pain. During our efforts, the European Association of Palliative Care guideline was recently published (16). In this guideline, the key messages and recommendations are essentially the same as in the Japanese guideline; but their recommendation levels are generally weak because of the lack of confirmatory evidence in the majority of fields. The results highlight the importance of conducting well-designed, controlled trials to identify the best practice in cancer pain management.

## Conflict of interest statement

None declared.

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## APPENDIX

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