JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2020, 50(5)586–593
doi: 10.1093/jjco/hyaa003
Advance Access Publication Date: 26 March 2020
Original Article

OXFORD

Original Article

JPOS/JASCC clinical guidelines for delirium in adult cancer patients: a summary of recommendation statements

Yoshinobu Matsuda[1], Hitoshi Tanimukai[2], Shinichiro Inoue[3], Shuji Inada[4], Koji Sugano[5], Hideaki Hasuo[6], Masafumi Yoshimura[7], Saho Wada[8], Chikako Dotani[9], Hiroyoshi Adachi[10], Yoshiaki Okamoto[11], Mari Takeuchi[12], Daisuke Fujisawa[13], Jun Kako[14], Chiyuki Sasaki[15], Yasuhiro Kishi[16], Nobuya Akizuki[17], Masatoshi Inagaki[18], Yosuke Uchitomi[19], Eisuke Matsushima[20], and Toru Okuyama[21,*]

[1]Department of Psychosomatic Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai, Japan, [2]Faculty of Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [3]Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Science, Okayama, Japan, [4]Department of Psychosomatic Medicine, The University of Tokyo Hospital, Tokyo, Japan, [5]Division of Respiratory Medicine, Juntendo Tokyo Koto Geriatric Medical Center, Tokyo, Japan, [6]Department of Psychosomatic Medicine, Kansai Medical University, Hirakata, Japan, [7]Department of Neuropsychiatry, Kansai Medical University, Moriguchi, Japan, [8]Department of Psycho-Oncology, National Cancer Center Hospital, Tokyo, Japan, [9]Department of Pediatrics, The University of Tokyo Hospital, Tokyo, Japan, [10]Sleep Medicine Center, Osaka University Hospital, Suita, Japan, [11]Department of Pharmacy, Ashiya Municipal Hospital, Ashiya, Japan, [12]Department of Palliative Care, Keio University School of Medicine, Tokyo, Japan, [13]Division of Patient Safety, Keio University School of Medicine, Tokyo, Japan, [14]Division of Nursing Science, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan, [15]Nursing Department, National Cancer Center Hospital, Tokyo, Japan, and [16]Department of Psychiatry, Nippon Medical School Musashikosugi Hospital, Kawasaki 211-8533, Japan, [17]Department of Psycho-Oncology/Psychiatry, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo 113-8677, Japan, [18]Department of Psychiatry, Faculty of Medicine, Shimane University, Izumo 693-8501, Japan, [19]Innovation Center for Supportive, Palliative and Psychosocial Care, National Cancer Center Hospital, Tokyo 104-0045, Japan, [20]Section of Liaison Psychiatry and Palliative Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo 113-8519, Japan, and [21]Division of Psycho-oncology and Palliative Care, Nagoya City University Hospital, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan

*For reprints and all correspondence: Toru Okuyama, Division of Psycho-Oncology and Palliative Care, Nagoya City University Hospital, Mizuho-cho, Mizuho-ku, Nagoya, Aichi 467-8601, Japan. E-mail: okuyama@med.nagoya-cu.ac.jp

Received 18 October 2019; Revised 30 December 2019; Editorial Decision 2 January 2020; Accepted 8 January 2020

Abstract

Background: The Japanese Psycho-Oncology Society and Japanese Association of Supportive Care in Cancer recently launched the clinical practice guidelines for delirium in adult cancer patients. The aim of the guidelines was to provide evidence-based recommendations for the clinical assessment and management of delirium in cancer patients. This article reports the process of developing the guideline and summarizes the recommendations made.

Methods: The guidelines were developed in accordance with the Medical Information Network Distribution Service creation procedures. The guideline development group, consisting of multidisciplinary members, formulated nine clinical questions. A systematic literature search was conducted to identify relevant articles published prior to through 31 May 2016. Each article was reviewed by two independent reviewers. The level of evidence and the strength of the recommendations were graded using the grading system developed by the Medical Information Network Distribution Service, following the concept of The Grading of Recommendations Assessment, Development and Evaluation system. The modified Delphi method was used to validate the recommendation statements.
Results: This article provides a summary of the recommendations with rationales for each, as well as a short summary.
Conclusions: These guidelines will support the clinical assessment and management of delirium in cancer patients. However, additional clinical studies are warranted to further improve the management of delirium.

Key words: delirium, cancer, guideline, palliative care, psycho-oncology

Introduction

Delirium is a common neuropsychiatric condition characterized by an acute onset of change in attention or awareness, accompanied by change in cognition (1). The prevalence of delirium in elderly patients with advanced lung cancer admitted to hospital for palliative care was 40% (2). Delirium was observed in 42 and 88% of the patients at the time of admission to the palliative care unit (PCU) and prior to death, respectively (3). Delirium is a distressing symptom for cancer patients, caregivers and medical staff (4,5). Therefore, assessing and managing delirium are important to improve the quality of life of cancer patients and their caregivers.

Several clinical guidelines for delirium have been published, which are mostly relevant to geriatric patients (6,7) or patients in the intensive care unit (8). Delirium in cancer patients is characterized by its causes and the trajectories of cancer and is often caused by medications (e.g. opioids and corticosteroids) frequently used in cancer setting (9). Several pathophysiological conditions related to cancer, such as hypercalcemia and brain metastasis, are also known to cause delirium (10). Furthermore, delirium at the end of life is often refractory to treatment; thus, specific goal-setting and management are required (11).

In addition, the available assessment tools for delirium and drugs to manage the symptom of delirium may vary among countries. Therefore, clinical questions have been raised based on the medical situation in Japan. Thus, the Japan Psycho-Oncology Society and Japanese Association of Supportive Care in Cancer decided to establish guidelines for delirium in adult patients with cancer by following a formal guideline development guide, including recommendations or descriptions for clinical questions that are of interest in Japan.

The target users of the guidelines are all healthcare professionals working with cancer patients. These guidelines do not address postoperative delirium in cancer patients or delirium in pediatric cancer patients. This is because recommendations for postoperative delirium may be available in other guidelines, and the assessment and management of delirium in pediatric cancer patients differ from those applied in adult patients. In this article, we describe the process of the developing these guidelines and present a summary of the recommendations for delirium in adult cancer patients along with the rationales for each.

Methods

Development process

The guidelines were prepared in accordance with the Medical Information Network Distribution Service 2014 system [http://minds4.jcqhc.or.jp/minds/guideline/handbook2014.html (in Japanese)]. The guideline development group consisted of multidisciplinary members (i.e. nine psychiatrists, three psychosomatic physicians, one oncologist, one pharmacist, one psychologist, and two nurses). The guideline development group formulated nine clinical questions (CQs) to be answered. Among them, five CQs (CQ 1, 2, 7, 8 and 9) were dealt with as background questions; hence, evidence levels and strength of recommendation were not produced. In general, it is recognized that background questions are better to avoid in the clinical guidelines. However, we decided to deal with these CQs because we thought it is important to reveal available evidence for these CQs and one of the purpose of these guidelines are to provide fundamental knowledge of delirium among medical staff who has little knowledge. Subsequently we conducted a systematic literature search for each CQ in four electronic databases (i.e. PubMed, the Cochrane Central Resister of Controlled Trial, Cochrane Database of Systematic Reviews and Ichushi-Web of the Japan Medical Abstracts Society), with searches limited to articles published prior to 31 May 2016 and written in English or Japanese. Search terms used for PubMed are indicated in Supplementary Table 1. In the case a limited number of articles (or none) investigating delirium in cancer patients were identified, we defined additional searches extended to articles concerning delirium in non-cancer patients. We identified the relevant studies in the following two steps. Firstly, two members of the taskforce independently reviewed each identified abstract to select studies meeting the rough eligibility criteria for each CQ (not shown). Secondly, full-text articles relating to studies identified during step 1 were screened according to the strict eligibility criteria. Additional articles were identified by hand search.

Drafting recommendations and the Delphi method

Two- or three-member teams from the taskforce drafted the recommendation statements for each CQ. The modified Delphi method was used to validate the draft recommendation statements. Delphi rounds were conducted by 13 psychiatrists, three psychosomatic physicians,

Table 1. Strength of recommendations

1 (strong)	Strong recommendation to do (or not to do) The benefit of the recommended treatment certainly overweighs the harm or burden In the guideline, statements are described using the term 'recommend'
2 (weak)	Weak recommendation to do (or not to do) The benefit of the recommended treatment may be closely balanced with the harm or burden In the guideline, statements are described using the term 'suggest'

Table 2. Level of evidence

A (high)	The evidence is established based on the results of studies. Further research is very unlikely to change our confidence in the estimate of effect. For example, high-quality randomized controlled trials with concordant results or a meta-analysis of randomized controlled trials
B (moderate)	Although some moderate-/high-quality studies support the result, the evidence is insufficient. Further research is likely to significantly impact our confidence in the estimate of effect and may change this estimate. For example, randomized controlled trials with inconsistent results, low-quality controlled trials, or high-quality observational trials with consistent results
C (low)	Although some low-quality studies support the result, the evidence is insufficient. Further research is very likely to significantly impact our confidence in the estimate of effect and is likely to change this estimate. For example, low-quality observational trials with consistent results
D (very low)	There is insufficient or no scientific evidence for the result. Any estimate of effect is very uncertain. For example, observational trials with inconsistent results, case reports, or expert opinions

one oncologist, one pharmacist, one psychologist, one nurse and 10 representatives from other specialties (i.e. two palliative care physicians, one pharmacist, three oncologists, one home care physician, one psychiatrist, one nurse and one representative of a cancer patient group). After two Delphi rounds and an external review conducted by three external reviewers (i.e. one palliative care physician, one oncologist and one representative of a cancer patient group), the final version of the recommendation statements was approved.

Evidence and recommendation levels

The evidence and the strength of the recommendations were graded using the grading system developed by the Medical Information Network Distribution Service, following the concepts of The Grading of Recommendations Assessment, Development and Evaluation system (Tables 1 and 2).

Results

CQ1. Which assessment tools for delirium are recommended for cancer patients?

Recommendations. 'There are no specific tools recommended, although the Memorial Delirium Assessment Scale (MDAS), Delirium Rating Scale-Revised-98 (DRS-R98), Communication Capacity Scale (CCS) and Agitation Distress Scale (ADS) have been reported as tools to detect delirium in cancer patients. The MDAS and DRS-R-98 are available to assess the severity of delirium. The CCS and ADS are available for patients in severe physical states.'

Lawlor et al. examined the reliability and validity of the MDAS ratings in 104 cancer patients admitted to a PCU (12). The findings showed that the sensitivity and specificity were 98 and 96%, respectively, when the cutoff value was 7 in the MDAS. Grassi et al. explored the usefulness of the DRS in assessing delirium in 105 cancer patients (13). They found that the sensitivity and specificity were 95 and 61% when a cutoff value of 10 was applied in the DRS, and 68 and 94% when a cutoff value of 13 was applied in the MDAS, respectively. Bosisio et al. analyzed the same data set as Grassi et al. and assessed the ability of all DRS and MDAS items to distinguish patients with from those without (14). The distribution of the MDAS item scores was significantly different in all items in the MDAS. In contrast, the distribution of the DRS item scores in 'Hallucinations' and 'Lability of mood' was not significantly different in the DRS. Meagher et al. developed the Delirium Motoric Checklist and examined which items were associated with hyperactive or hypoactive delirium, proposing criteria for the hyperactive and hypoactive motor subtypes (15). Morita et al. examined whether the CCS and ADS are valid and reliable tools to measure the severity of delirium in 30 terminally ill cancer patients with delirium and found the scales to be acceptable (16). Leonard et al. conducted a systematic review (SR) of studies regarding the assessment tools for delirium in palliative care (17). The group reported that the Confusion Assessment Scale (CAM), MDAS, Bedside Confusion Scale, CCS and ADS are validated assessment tools in palliative care. Furthermore, their findings revealed that the CAM, Nursing Delirium Screening Scale (Nu-DESC) and Single Question in Delirium are appropriate to use as screening tools for delirium, while the MDAS and DRS-R-98 are appropriate to assess the severity of delirium.

Existing research studies indicate that the MDAS or DRS is useful in determining the severity of delirium; however, they are characterized by suboptimal accuracy for the detection of delirium. Although the reliability and validity of the Japanese version of these two scales have been confirmed (18,19), there are several barriers to implementing these scales in clinical practice. Firstly, the use of these scales requires specific training of the medical staff. Secondly, it is difficult to use these scales for patients in severe physical status, as they include several items which require the cooperation of patients. The CCS and ADS have been developed for use in the palliative care setting and were designed to overcome these shortcomings. However, larger studies are warranted to validate the usefulness of these scales. Moreover, the usefulness of the CCS and ADS as diagnostic or screening scales has not been examined. Similarly, the reliability and validity of the Japanese version of the Nu-DESC and the Single Question in Delirium have not been evaluated. Furthermore, thus far, studies have not investigated the usefulness of the CAM in cancer patients.

CQ2. What are the common precipitating factors of delirium in cancer patients?

Recommendation. 'Physical complications (e.g. dehydration, hypoalbuminemia, infection and hypoxic encephalopathy) and medications (e.g. opioids) may cause delirium in cancer patients.'

Gaudreau et al. conducted a prospective observational study to examine the association between exposure to anticholinergics, ben-

zodiazepines, corticosteroids and opioids and the risk of delirium in 261 cancer patients (9). Opioids, corticosteroids and benzodiazepines were independently associated with an increased risk of delirium. Gaudreau et al. also conducted a prospective observational study to determine whether exposure to corticosteroids, benzodiazepines or opioids predicted delirium in 114 cancer patients (20). Opioids were significantly associated with an increased risk of delirium. Lawlor et al. conducted a retrospective study to examine the precipitating factors in 114 cancer patients admitted to a PCU (3). They found that delirium precipitated by psychoactive medications, including opioids, was significantly associated with reversibility, while hypoxic encephalopathy and non-respiratory infection were significantly associated with non-reversibility. Ljubisavljevic et al. conducted a prospective observational study to examine baseline factors associated with the development of delirium in 113 cancer patients (21). In the multivariate analysis, advanced age, cognitive impairment, low level of albumin, bone metastases and the presence of hematological malignancy were significantly associated with the development of delirium. Sagawa et al. conducted a prospective observational study to examine the causes of delirium in cancer patients with delirium (22). Opioids, inflammation, dehydration and/or abnormalities in the level of sodium were the frequent causes of delirium. Morita et al. conducted a prospective observational study to examine the risk factors for delirium based on the Diagnostic and Statistical Manual of Mental Disorders-IV in 150 terminal cancer patients in hospice (23). In the multivariate analysis, poor Palliative Performance Status, ≥10 physical symptoms, and opioids were significantly associated with the incidence of delirium.

These six studies were heterogeneous in terms of the study design, patients and outcomes. However, five of those reported an association between opioids and delirium. Therefore, opioids are one of the most important causes of delirium in cancer patients. Although the results were inconsistent, other causes (e.g. benzodiazepines, corticosteroids, poor performance status, dehydration, electrolyte imbalance, hypoalbuminemia, infection and hypoxemic encephalopathy) were also associated with delirium.

CQ3. Are antipsychotics recommended to improve symptoms of delirium in cancer patients?

Recommendation. 'Antipsychotics are suggested to use in cancer patients with delirium (2C).'

Agar et al. conducted an randomized controlled trial (RCT) to determine the efficacy of risperidone or haloperidol relative to placebo in relieving the target symptoms of delirium associated with distress (sum of Nu-DESC behavioral, communication and perceptual items) in 247 patients receiving palliative care (cancer patients: 88%) (24). The delirium symptom scores in the antipsychotic groups were significantly higher than the scores recorded in the placebo group. Also, significantly more extrapyramidal effects were observed in the antipsychotic groups. The haloperidol group was associated with significantly shorter survival versus the placebo group. Kishi et al. conducted a prospective study to evaluate the effectiveness of risperidone against delirium in 29 cancer patients (25). The DRS-R98 severity scale score significantly improved from baseline to Day 7, and 38% of the patients achieved remission. None of the patients experienced extrapyramidal symptoms, while one patient experienced mild sedation. Elsayem et al. conducted a prospective study to determine the safety and tolerability of subcutaneous olanzapine for hyperactive or mixed delirium in 24 cancer patients (26). A score of ≤1 on the Richmond Agitation-Sedation Scale (RASS) was achieved in 38% of the patients. Probable systemic adverse events were observed in four patients. Of all patients, 30% experienced sedation. Breitbart et al. conducted a trial of olanzapine for delirium in 79 cancer patients (27). Olanzapine significantly improved the severity of delirium in the MDAS scores. None of the patients experienced extrapyramidal symptoms. Watanabe et al. conducted a prospective observational study to evaluate the effectiveness of quetiapine for delirium in 21 cancer patients (28). They reported that the mean DRS-R98 score significantly improved; however, the timing of outcome assessment was not mentioned. Drowsiness and dizziness were noted in one case each. Neufeld conducted a SR and meta-analysis (MA) to evaluate the use of antipsychotics for preventing and treating delirium in non-cancer patients (29). Eleven studies, including eight RCTs, were included in this MA. The use of antipsychotics was not associated with change in delirium duration and severity, with high heterogeneity observed among the studies.

We found one RCT reporting lack of efficacy of antipsychotics for delirium and four before–after studies reporting effectiveness of antipsychotics against delirium. Regarding the RCT conducted by Agar et al., the enrolled patients were terminally ill and near death, and they had mild-to-moderate delirium. Therefore, caution must be exercised in generalizing these results to all cancer patients with delirium. In addition, the primary endpoint of this study was assessed using an assessment tool whose validity and reliability were not evaluated. Therefore, we decided to downgrade the evidence level considered for this study in this clinical question. In addition, the MA conducted by Neufeld et al. included only one preliminary placebo-controlled trial.

Thus, we suggested that antipsychotics are to be used in cancer patients with delirium. A specific approach is necessary for the management of delirium in terminally ill cancer patients. Therefore, we should carefully consider the use of antipsychotics in terminally ill cancer patients with delirium (see CQ8).

CQ4. Is hydroxyzine recommended to improve symptoms of delirium in cancer patients?

Recommendation. 'Hydroxyzine is suggested not to be used (2D).'

We did not identify studies in cancer patients or SR/RCT in non-cancer patients investigating the effectiveness of hydroxyzine on delirium symptoms. Thus, we suggested that hydroxyzine is not to be used.

CQ5. Is benzodiazepine recommended to improve the symptoms of delirium in cancer patients?

Recommendation. 'Benzodiazepines alone are suggested not to be used (2C).'

We did not identify studies in cancer patients or SR/RCT in non-cancer patients investigating the effectiveness of benzodiazepines alone on delirium.

In addition, some studies reported an association between benzodiazepines and the occurrence or worsening of delirium (9,30). Thus, we suggested that benzodiazepines alone are not to be used.

CQ6. Is opioid switching recommended in cancer patients with delirium caused by opioids to improve the symptom of delirium?

Recommendation. 'Opioid switching is suggested to be performed (2C).'

Morita et al. conducted an open-label trial to examine the efficacy of opioid switching (i.e. from morphine to fentanyl) in 21 cancer

patients with morphine-induced delirium in the PCU (31). The mean MDAS score significantly decreased from Day 0 to Day 3 and from Day 0 to Day 7. Moryl et al. conducted an open-label, non-randomized study to document the use of methadone as part of an opioid switching strategy in 20 patients with uncontrolled pain and severe delirium admitted to a cancer palliative care hospital (32). The MDAS showed improvement from baseline to 3 days after switching; however, a statistical analysis was not performed. Benitez-Rosario et al. conducted a prospective study to assess the efficacy and safety of a protocol of opioid rotation from transdermal fentanyl to methadone in 17 cancer patients admitted to the PCU (33). Of the five patients who experienced delirium at baseline, four patients achieved reversion of delirium in approximately 6 days. Gagnon et al. conducted a prospective observational study investigating the effect of intermittent subcutaneous injection of oxycodone in patients for whom opioid switching from morphine or hydromorphone was indicated, in an attempt to reverse delirium, improve pain control, or decrease side effects induced by other opioids (34). Thirty-eight patients were switched to oxycodone due to delirium, and the delirium was reversed in 13 of those patients (34%). Maddocks et al. conducted a prospective study to confirm that opioid switching from morphine to subcutaneous injection of oxycodone improved delirium in 19 cancer patients in a hospice (35). Of the 13 patients who completed this study, nine patients (69%) did not fulfill the criteria for delirium 6 days after opioid switching. Takigawa et al. conducted a prospective observational study to evaluate the effectiveness of partial opioid switching from morphine to intravenous compound oxycodone for the treatment of morphine-induced delirium in advanced cancer patients (36). In 27 patients, the MDAS score significantly improved after partial switching. Morita et al. conducted a historical control study to clarify the effects of partial opioid switching from morphine to fentanyl and hydration on the occurrence of agitated delirium in patients with final stage of cancer (164 patients in 1996–1997 and 120 patients in 2000–2001, 37). Partial opioid switching to fentanyl and moderate levels of hydration had no significant preventive effects on the occurrence of agitated delirium in the last week of life.

All six before–after studies reported that opioid switching was effective against delirium in cancer patients, with the exception of one historical control study conducted by Morita et al., which reported that partial opioid switching had no preventive effect on the occurrence of agitated delirium.

Thus, we suggested that opioid switching is to be performed. In patients with delirium caused by morphine, opioid switching to other opioids is weakly recommended; however, we were unable to determine the most appropriate which opioid for the switch from morphine. There were two studies in which the opioids were switched to methadone; therefore, methadone is an option for switching considering the individual medical needs of patients.

CQ7. Which non-pharmacological interventions are recommended to improve symptoms of delirium in cancer patients?

Recommendation. 'Non-pharmacological interventions include reorientation, early mobilization and intervention targeting the risk factors of delirium, such as visual impairment, hearing impairment and environmental manipulation.'

Tatematsu et al. conducted a retrospective study of 48 cancer patients who were referred to the palliative care team (38). The patients were divided into two groups (exercise therapy or non-exercise therapy) according to the use of exercise therapy for early ambulation at the time delirium had occurred. The dose of antipsychotics was significantly lower in the exercise therapy group. Abraha et al. conducted a systematic overview of SRs of comparative studies concerning non-pharmacological interventions for the management or prevention of delirium in older patients (39). They reported that multicomponent non-pharmacological interventions significantly reduced the incidence of delirium in surgical and medical wards. For patients with delirium, the available evidence does not support the efficacy of multicomponent non-pharmacological interventions. The multicomponent non-pharmacological interventions included reorientation, early mobilization, family education, environmental stimuli, etc. Britton et al. conducted a SR to examine the effectiveness of multidisciplinary team interventions in elderly patients with delirium superimposed on an underlying chronic cognitive impairment (40). However, there are no studies focusing on patients with prior cognitive impairment; thus, the management of delirium in this group could not be assessed. Hshieh et al. conducted a SR and MA to evaluate the available evidence regarding multicomponent non-pharmacological interventions for reducing the incidence of delirium and preventing poor outcomes associated with delirium (41). Four randomized or matched trials reduced the incidence of delirium incidence and the rate of falls. Multicomponent non-pharmacological interventions included orientation, early mobilization, providing hearing and visual aids, preservation of the sleep–wake cycle and hydration. Siddiqi et al. conducted a SR and MA to examine the effectiveness of interventions for preventing delirium in patients hospitalized in a non-intensive care unit (42). They found that multicomponent interventions reduced the incidence of delirium compared with usual care.

Few studies have investigated the effectiveness of non-pharmacological interventions on the incidence or severity of delirium in cancer patients. We considered that non-pharmacological interventions developed for non-cancer patients may be applicable to patients with cancer because this type of intervention is not linked to risk of harm. One retrospective study of exercise therapy in cancer patients assessed the dose of antipsychotics; however, it did not assess delirium. The effectiveness of multicomponent non-pharmacological interventions on the incidence, but not the severity, of delirium has been reported in non-cancer settings.

CQ8. Which interventions are recommended to improve symptoms of delirium in terminally ill cancer patients?

Recommendation. 'Antipsychotics are not recommended as first-line management for mild-to-moderate delirium in terminally ill cancer patients.'

'Antipsychotics may be indicated for severe hyperactive delirium in terminally ill cancer patients.'

'When antipsychotics alone are not effective against severe hyperactive delirium in terminally ill cancer patients, the combination of a benzodiazepine and an antipsychotic may be a management option.'

'Hydration and opioid switching may be considered as a mean to relieve delirium in terminally ill cancer patients.'

Pharmacological management Agar et al. conducted an RCT to determine the efficacy of risperidone or haloperidol versus placebo to treat delirium in patients receiving palliative care (24) (see CQ3). Hui et al. conducted a double-blind RCT at an acute PCU to compare the efficacy of lorazepam versus placebo as an adjuvant to

haloperidol for the management of persistent agitation in terminally ill advanced cancer patients with delirium (43). The addition of lorazepam to haloperidol resulted in a significantly greater reduction in agitation (RASS) at 8 hours compared with haloperidol alone. Moreover, the addition of lorazepam to haloperidol caused greater sedation than haloperidol alone. Elsayem et al. conducted a prospective study to determine the safety and tolerability of subcutaneous olanzapine in the management of hyperactive or mixed delirium in advanced cancer patients (26) (see CQ3).

Hydration Cerchietti et al. conducted an RCT to examine the usefulness of hypodermoclysis in the control of thirst, chronic nausea and delirium in 42 terminally ill cancer patients who had at least one of these three symptoms (44). At baseline, seven patients in the intervention group and eight patients in the control group had delirium. The mean score of the Mini Mental State Examination did not change significantly between baseline and 24 or 48 hours after hypodermoclysis. Bruera et al. conducted an RCT to determine the usefulness of parenteral hydration (normal saline 1 l per day) compared with placebo (normal saline 100 ml per day) daily in changing the sum of four dehydration symptoms (i.e. fatigue, myoclonus, sedation and hallucinations) in 129 cancer patients in hospice care (45). There were no significant differences observed in delirium scores between the two groups. However, the placebo group showed significantly greater deterioration from baseline in the nighttime Nu-DESC scores at Day 4.

Opioid switching We identified three articles regarding opioid switching in delirium in the terminal cancer setting (32,36,37) (see CQ 6).

Celiac plexus block (CPB) Arai et al. conducted an observational study to examine the effectiveness of the addition of a CPB to pharmacotherapy for pain on the occurrence and duration of delirium in 19 patients with pancreatic cancer, compared with a historical control of 17 patients who received pharmacotherapy alone (46). Both the occurrence and duration of delirium were reduced in the CPB group compared with those observed in the control group. The opioid doses in the CPB group were significantly lower than those reported in the historical control, suggesting that the opioid dosage is a confounding factor.

Regarding pharmacotherapy, the study conducted by Agar et al. was the only RCT that evaluated the efficacy of antipsychotics against delirium mainly in patients with terminal cancer. In this study, there was no significant efficacy observed in the antipsychotic groups compared with the placebo group. As mentioned in the CQ3 section, this study had some limitations, e.g. most of the patients had mild-to-moderate delirium. Hui et al. and Elsayem et al. conducted studies in patients with uncontrolled delirium despite management with haloperidol. We decided to adopt the study conducted by Hui et al. as evidence in this CQ, although the primary outcome of their study (RASS) did not include all delirium symptoms (only agitation). On the other hand, we decided not to adopt the study conducted by Elsayem et al. as evidence for CQ8 due to the lack of statistical analysis of the effect of management on delirium. By summarizing this evidence, we decided not to recommend the use of antipsychotics in patients with mild-to-moderate delirium. According to the evidence regarding the use of antipsychotics against delirium in nonterminal cancer patients, the use of antipsychotics can be considered in cases with hyperactive and severe symptoms of delirium. Based on the study conducted by Hui et al. in patients experiencing delirium that was hyperactive and refractory to management with antipsychotics, addition of a benzodiazepine in combination with an antipsychotic is an option for managing agitation.

The two identified RCTs regarding hydration were not designed to primarily investigate the efficacy of hydration on delirium. On the other hand, it has been established that dehydration is one of the modifiable causes of delirium and that this type of delirium can be resolved through hydration. Considering these findings, we suggest hydration as a treatment option in terminally ill cancer patients for whom dehydration is considered the main cause of delirium. CPB can be a treatment option for patients with pain and delirium. We decided not to adopt this study as evidence for CQ8 as the level of evidence was very low.

CQ9. What is the support that is preferred by the family of cancer patients with delirium?

The support that is preferred by the family of cancer patients with delirium includes specific support for delirium, information support and nonspecific general support.

Namba et al. conducted a single-center qualitative study in 20 bereaved family members of cancer patients who developed delirium during the last 2 weeks prior to death (47). They identified the following three main components of the support recommended by bereaved family members: (i) specific support for delirium (i.e. 'respect patients' subjective world,' 'treat patients as same as before developing delirium,' 'facilitate family's preparations for the patients' death' and 'relieve family's physical and psychological burden'); (ii) information support (i.e. provide information on the causes, pathologies, possible treatments and expected course, instruct family how to treat the patients in delirium and inform family that delirium is a common phenomenon); and (iii) nonspecific general support (i.e. symptom control, human attitude of the medical staff, high-quality professional care, prompt response and excellent teamwork and good environment).

Discussion

These are the first guidelines for delirium in adult cancer patients addressing important topics in Japan following a formal guideline development guide. Although other international guidelines for delirium in cancer patients have been published, the present guidelines involving tailored clinical questions play an important role in oncological and palliative care practice in Japan. For example, in CQ1 we described the availability of the Japanese version of assessment tools for delirium; in CQ4 we addressed hydroxyzine as it is sometimes used for the management of hyperactive symptoms of delirium in palliative care setting in Japan; and in CQ9 we described opinions based on a survey of bereaved family members of Japanese cancer patients.

We consider that the dissemination of these guidelines is important; thus, the Japanese version of guideline will be available to all (i.e. open access). These guidelines are scheduled to undergo revision every 3 years. In the future, we would like to include new clinical questions currently not included in these guidelines, such as prophylaxis interventions for delirium. Additional high-quality clinical studies are warranted to manage delirium in adult patients with cancer.

In conclusion, these guidelines will support the clinical assessment and management of delirium in Japanese adult cancer patients. However, additional clinical studies are warranted to further improve the management of delirium.

Acknowledgments

The development of these guidelines was greatly assisted by the following individuals: Fumio Nagashima, Mayumi Noda and Sen Yamakawa (external reviewers); Shinsuke Amano (the Group Nexus Japan), Etsuko Ariga (Japan Society of Clinical Oncology), Yuya Ise (Japanese Society for Pharmaceutical Palliative), Toshiaki Saeki (Japanese Cancer Association), Jiichiro Sasaki (Japanese Society of Medical Oncology), Hiroshi Suzuki (Japanese Academy of Home Care Physicians), Nobuhisa Nakajima (Japanese Society for Palliative Medicine), Kotaro Hatta (Japanese Society of General Hospital Psychiatry) and Toru Mukouhara (Japanese Society of Cancer Nursing, and Care and Sciences) (Delphi members); and Fujimi Kawai, Yumi Watanabe and Yurika Sato (literature researcher).

Supplementary material

Supplementary material is available at *JJCOJ* online.

Conflict of interest statement

Dr. Adachi received a grant from Eisai Co., Ltd. outside the submitted work as well as lecture fees from MSD K.K. and Eisai Co., Ltd. outside the submitted work. Dr. Kishi reports receiving honoraria from Shionogi & Co., Ltd., Merck Sharp & Dohme, Otsuka, Pfizer, Mochida, Eli Lilly, Daiichi-Sankyo Co., Ltd., Eisai Co., Ltd., Dainihon-Sumitomo, Tanabe-Mitsubishi and Tsumura as well as serving as a consultant for Meiji and Merck Sharp & Dohme. Dr. Inagaki has received lecture fees from Meiji, Mochida, Takeda, Novartis, Yoshitomi, Pfizer Japan Inc., Eisai Co., Ltd, Otsuka, MSD and Sumitomo Dainippon and personal fees from Technomics. Dr. Inagaki has also received research funds from Novartis. Dr. Okuyama reports receiving grants from the Ministry of Health, Labour and Welfare, Japan, and the Japanese Society for the Promotion of Science. During the conduct of the study, personal fees (outside the submitted work) were received from the following companies: Chugai Pharmaceutical Co., Ltd., MSD K.K., Daiichi-Sankyo Co., Ltd, Shionogi & Co., Ltd, Pfizer Japan Inc. and Terumo Corporation.

Funding

This work was funded by the Japan Psycho-Oncology Society and was supported in part by Health, Labour and Welfare Sciences Research Grants: Research for Promotion of Cancer Control Programmes (19EA1009).

References

1. Association AP. *Diagnostic and Statistical Manual of Mental Disorders, 5th edn: DSM-5*. American Psychiatric Publishing, 2013.
2. Uchida M, Okuyama T, Ito Y *et al.* Prevalence, course and factors associated with delirium in elderly patients with advanced cancer: a longitudinal observational study. *Jpn J Clin Oncol* 2015;45:934–40.
3. Lawlor PG, Gagnon B, Mancini IL *et al.* Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000;160:786–94.
4. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics* 2002;43:183–94.
5. Bruera E, Bush SH, Willey J *et al.* Impact of delirium and recall on the level of distress in patients with advanced cancer and their family caregivers. *Cancer* 2009;115:2004–12.
6. Tropea J, Slee JA, Brand CA *et al.* Clinical practice guidelines for the management of delirium in older people in Australia. *Australas J Ageing* 2008;27:150–6.
7. Brajtman S, Wright D, Hogan DB *et al.* Developing guidelines on the assessment and treatment of delirium in older adults at the end of life. *Can Geriatr J* 2011;14:40–50.
8. Barr J, Fraser GL, Puntillo K *et al.* Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263–306.
9. Gaudreau JD, Gagnon P, Harel F *et al.* Psychoactive medications and risk of delirium in hospitalized cancer patients. *J Clin Oncol* 2005;23:6712–8.
10. Bush SH, Lawlor PG, Ryan K *et al.* Delirium in adult cancer patients: ESMO clinical practice guidelines. *Ann Oncol* 2018;29:iv143–iv65.
11. Okuyama T, Yoshiuchi K, Ogawa A *et al.* Current pharmacotherapy does not improve severity of hypoactive delirium in patients with advanced cancer: pharmacological audit study of safety and efficacy in real world (phase-R). *Oncologist* 2019;24:e574–e82.
12. Lawlor PG, Nekolaichuk C, Gagnon B *et al.* Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: assessing delirium in advanced cancer. *Cancer* 2000;88:2859–67.
13. Grassi L, Caraceni A, Beltrami E *et al.* Assessing delirium in cancer patients: the Italian versions of the delirium rating scale and the memorial delirium assessment scale. *J Pain Symptom Manag* 2001;21:59–68.
14. Bosisio M, Caraceni A, Grassi L, Italian Delirium Study G. Phenomenology of delirium in cancer patients, as described by the memorial delirium assessment scale (MDAS) and the delirium rating scale (DRS). *Psychosomatics* 2006;47:471–8.
15. Meagher D, Moran M, Raju B *et al.* A new data-based motor subtype schema for delirium. *J Neuropsychiatry Clin Neurosci* 2008;20:185–93.
16. Morita T, Tsunoda J, Inoue S *et al.* Communication capacity scale and agitation distress scale to measure the severity of delirium in terminally ill cancer patients: a validation study. *Palliat Med* 2001;15:197–206.
17. Leonard MM, Nekolaichuk C, Meagher DJ *et al.* Practical assessment of delirium in palliative care. *J Pain Symptom Manag* 2014;48:176–90.
18. Matsuoka Y, Miyake Y, Arakaki H *et al.* Clinical utility and validation of the Japanese version of memorial delirium assessment scale in a psychogeriatric inpatient setting. *Gen Hosp Psychiatry* 2001;23:36–40.
19. Kato M, Kishi Y, Okuyama T *et al.* Japanese version of the delirium rating scale, revised-98 (DRS-R98-J): reliability and validity. *Psychosomatics* 2010;51:425–31.
20. Gaudreau JD, Gagnon P, Roy MA *et al.* Opioid medications and longitudinal risk of delirium in hospitalized cancer patients. *Cancer* 2007;109:2365–73.
21. Ljubisavljevic V, Kelly B. Risk factors for development of delirium among oncology patients. *Gen Hosp Psychiatry* 2003;25:345–52.
22. Sagawa R, Akechi T, Okuyama T *et al.* Etiologies of delirium and their relationship to reversibility and motor subtype in cancer patients. *Jpn J Clin Oncol* 2009;39:175–82.
23. Tatsuya Morita JT, Inoue S. The risk factors for delirium in terminal cancer patients: a prospective study. *J Clin Psychiatry* 1998;40:823–9.
24. Agar MR, Lawlor PG, Quinn S *et al.* Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern Med* 2017;177:34–42.
25. Kishi Y, Kato M, Okuyama T *et al.* Treatment of delirium with risperidone in cancer patients. *Psychiatry Clin Neurosci* 2012;66:411–7.
26. Elsayem A, Bush SH, Munsell MF *et al.* Subcutaneous olanzapine for hyperactive or mixed delirium in patients with advanced cancer: a preliminary study. *J Pain Symptom Manag* 2010;40:774–82.
27. Breitbart W, Tremblay A, Gibson C. An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics* 2002;43:175–82.

28. Akira Watanabe YN, Kuroda T, Fukui K. Effectiveness of treatment using quetiapine for delirium in palliative care. *Jpn J Gen Hosp Psychiatry* 2016;23:277–86.
29. Neufeld KJ, Yue J, Robinson TN *et al.* Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2016;64:705–14.
30. Breitbart W, Marotta R, Platt MM *et al.* A double-blind trial of haloperidol, chlorpromazine, and lorazepam in the treatment of delirium in hospitalized AIDS patients. *Am J Psychiatry* 1996;153:231–7.
31. Morita T, Takigawa C, Onishi H *et al.* Opioid rotation from morphine to fentanyl in delirious cancer patients: an open-label trial. *J Pain Symptom Manag* 2005;30:96–103.
32. Moryl N, Kogan M, Comfort C *et al.* Methadone in the treatment of pain and terminal delirum in advanced cancer patients. *Palliat Support Care* 2005;3:311–7.
33. Benitez-Rosario MA, Feria M, Salinas-Martin A *et al.* Opioid switching from transdermal fentanyl to oral methadone in patients with cancer pain. *Cancer* 2004;101:2866–73.
34. Gagnon B, Bielech M, Watanabe S *et al.* The use of intermittent subcutaneous injections of oxycodone for opioid rotation in patients with cancer pain. *Support Care Cancer* 1999;7:265–70.
35. Maddocks I, Somogyi A, Abbott F *et al.* Attenuation of morphine-induced delirium in palliative care by substitution with infusion of oxycodone. *J Pain Symptom Manag* 1996;12:182–9.
36. Chizuko Takigawa YK, Ueda K, Morimoto Y. Efficacy of partial opioid rotation of morphine to intravenous compound oxycodone for morphine-induced delirium in advanced cancer patients. *JJSPC* 2009;6:557–63.
37. Morita T, Tei Y, Inoue S. Agitated terminal delirium and association with partial opioid substitution and hydration. *J Palliat Med* 2003;6:557–63.
38. Tatematsu N, Hayashi A, Narita K *et al.* The effects of exercise therapy on delirium in cancer patients: a retrospective study. *Support Care Cancer* 2011;19:765–70.
39. Abraha I, Trotta F, Rimland JM *et al.* Efficacy of non-pharmacological interventions to prevent and treat delirium in older patients: a systematic overview. The SENATOR project ONTOP series. *PLoS One* 2015;10:e0123090.
40. Britton A, Russell R. Multidisciplinary team interventions for delirium in patients with chronic cognitive impairment. *Cochrane Database Syst Rev* 2004;2:CD000395.
41. Hshieh TT, Yue J, Oh E *et al.* Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med* 2015;175:512–20.
42. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing* 2006;35:350–64.
43. Hui D, Frisbee-Hume S, Wilson A *et al.* Effect of Lorazepam with haloperidol vs haloperidol alone on agitated delirium in patients with advanced cancer receiving palliative care: a randomized clinical trial. *JAMA* 2017;318:1047–56.
44. Cerchietti L, Navigante A, Sauri A *et al.* Hypodermoclysis for control of dehydration in terminal-stage cancer. *Int J Palliat Nurs* 2000;6:370–4.
45. Bruera E, Hui D, Dalal S *et al.* Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Oncol* 2013;31:111–8.
46. Arai YC, Nishihara M, Kobayashi K *et al.* Neurolytic celiac plexus block reduces occurrence and duration of terminal delirium in patients with pancreatic cancer. *J Anesth* 2013;27:88–92.
47. Namba M, Morita T, Imura C *et al.* Terminal delirium: families' experience. *Palliat Med* 2007;21:587–94.