Intensive Palliative Care for Delirium, Dyspnea, and Pain: Before the diagnosis of the symptoms as being refractory

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Delirium

Outline (Table 1)

No method to prevent delirium in the terminal phase has been established, and it is important to detect delirium in the early stage and manage it before it becomes severe. Patients should be examined, considering that attention deficit (being distracted when being addressed, no adequate response) and sleep-wake rhythm disturbance (being unable to sleep at night, drowsing in the daytime) are observed in most patients. The presence of disorientation for date or place is often evaluated as delirium screening (e.g., “Do you know where is here?”), but the incidence of disorientation is approximately three quarters, and asking about disorientation without consideration may hurt patients; therefore, it should not be performed easily.

If delirium is diagnosed, its etiology should be clarified. The goal of treatment should be established based on the possibility of recovery. Frequent etiological factors for delirium in the terminal phase, in which delirium may become difficult to recover, include drugs (opioids, steroids, benzodiazepines, anticholinergic agents), organ damage (hypoxic encephalopathy, liver failure, renal failure), hypercalcemia, intracranial lesions, dehydration, and infection. Treatment of the etiology may help to relief delirium.

For treatment, uncomfortable physical symptoms, body movement restriction, and sensory deprivation, which are inducers that deteriorate delirium, should be managed. For pharmacological management, antipsychotics are primarily selected. If there is no response, the drug should be switched to another antipsychotic. If patients cannot maintain sleep, benzodiazepines (including orexin receptor antagonists if oral administration is possible) should be concomitantly used.

The contents to be reviewed in patients with difficult delirium are shown in Table 2, although all are not listed.

Table 1　Outline of delirium treatment

	Points	Management cases
Identification of an etiological factor and treatment	Identification of an etiological factor	Drug history/cerebral imaging procedures are confirmed, and measurement of oxygen saturation and a blood test are performed.
	Treatment for etiological factors that can be treated	Bisphosphonate is administered to treat hypercalcemia.
	Dose-reduction /discontinuation of causative drugs	The doses of opioids, steroids, benzodiazepines, and anticholinergic drugs are decreased, or these drugs are switched.
Establishment of the goal of treatment	It should be established which of two options: recovery and partial symptom relief, is targeted.	In patients with delirium caused by organ damage, recovery cannot be targeted, and get enough sleep at night and relief of irritation/agitation are targeted in many cases. The balance between the level of consciousness or communication and symptom relief should be considered.
Alleviation of factors involved in distress deterioration and care	Relief of uncomfortable physical symptoms	Pain, dyspnea, and fever are controlled, and fecal impaction or urinary retention is confirmed.
	Minimization of body movement restriction	The withdrawal of continuous drip infusion is considered, and routes/drains are arranged.
	Arrangement for sensory deprivation	The use of glasses/hearing aids, lighting adjustment (e.g., dim light at night), offering clues to the date/time (e.g., installation of a calendar/clock), and provision of a friendly environment (meeting with the family, management by the same health care professionals) are promoted.
Medical treatment	Pharmacological management	Typical (e.g., haloperidol) or atypical (e.g., risperidone, quetiapine) antipsychotic drugs are administered. If patients cannot maintain sleep, benzodiazepines should be concomitantly used.

Table 2. The contents to be reviewed in patients with difficult delirium

Identification of an etiological factor and treatment -An etiological factor should be estimated, and an etiology that may recover should be reviewed. -An etiology that can be treated (e.g., hypercalcemia, infection, dehydration) should be confirmed, and treatment should be performed. -If the involvement of opioids in the deterioration of delirium is suggested, analgesic methods should be reviewed (see Chapter Pain). -The necessity of a steroid, benzodiazepine, or anticholinergic drug should be reviewed. If it is not necessary, its dose should be decreased, or the administration should be discontinued. **Establishment of the goal of treatment** -The goal of treatment that may be achieved realistically should be discussed with the patient. Enough sleep at night and the relief of irritation/agitation should be initially targeted. **Alleviation of factors involved in distress deterioration and care** -Physical symptoms deteriorating delirium (pain, dyspnea, fever, fecal impaction, urinary retention) should be managed. -Management requiring body movement restriction (continuous drip infusion, routes/drains) should be reviewed. -Orientation support and environmental arrangement should be performed. **Medical treatment** -An antipsychotic should be administered. If there is no response, it should be switched to another antipsychotic. -If sleep is not enough at night or disturbed by irritation/agitation during the daytime, benzodiazepines should be concomitantly used.

Identification of an etiological factor and treatment

1. Identification of an etiological factor

Etiological factors for delirium can be classified into 3 types (Table 3): direct risk factors, precipitating factors (not direct etiologies, but factors promoting onset and contributing to a serious or protracted condition), and predisposing factors (a state in which brain hypofunction, as the pathogenesis of delirium, may occur) are essentially

present. Direct risk factors and precipitating factors should be treated as much as possible, then it is important to identify the etiology of delirium or factors contributing to deterioration.

In many patients with advanced cancer, several etiologies are present; 2 to 3 factors are involved in the appearance of delirium. Frequent etiological factors include drugs (opioids, steroids, benzodiazepines, anticholinergic drugs), organ damage (hypoxic encephalopathy, liver failure, renal failure), hypercalcemia, intracranial lesions (brain metastasis/carcinomatous meningitis), dehydration, infection, hyponatremia, and anemia. Therefore, frequent etiologies should be evaluated by reviewing the drug history, physical findings, hematological data, oxygen saturation, and brain imaging findings. Concerning hematological parameters, screening for etiologies that are frequent among hematological/blood biochemistry parameters is possible. If no other etiology is detected, the Vit. B group and thyroid function should be included.

The presence of abnormal findings does not always mean that these are the causes of delirium. If a finding deteriorates before the onset of delirium, or if the causative drug has been started or its dose has been increased before the onset of delirium, it may be an etiological factor. If an etiological factor is present before the appearance of delirium (time anticipation), and if delirium further deteriorates with the enhancement of the factor (dose-response dependency), it may be an etiological factor. For example, hyponatremia can be regarded as an etiological factor in patients who were alert when the sodium level was 131 mmol/L but had symptoms of delirium when the sodium level was 122 mmol/L, and in whom delirium reduced with sodium normalization during the subsequent course. However, other factors may also change at the same time, or factors other than clinical examination parameters may be involved; it is often difficult to identify an etiological factor, even if the evaluation for it was based on a longitudinal course. Therefore, it is practical to pick up all factors that may be etiologically involved.

Etiology investigation depends on the curability of the etiology. If etiology identification contributes to the causal treatment that the patient wishes, it should be promoted. On the other hand, if a disease-progression-related etiology is clear, and if it is not consistent with the patient's goal of treatment, it may not be necessary to comprehensively investigate individual etiologies. For example, if dominant jaundice that was suspected to be obstructive jaundice is present, and if the patient wishes to

undergo a jaundice-reducing procedure, the investigation should be promoted. On the other hand, if liver failure that was suspected to be caused by multiple liver metastases is present, and if the patient does not wish for examination or treatment, the etiology may be estimated based on the clinical course without conducting a new examination.

Table 3 Direct risk factors, precipitating factors, and predisposing factors for delirium in patients with advanced cancer

Direct risk factors	Frequent	Drugs (opioids, steroids, benzodiazepines, anticholinergic drugs) Organ damage (respiratory failure, liver failure, renal failure) Hypercalcemia Intracranial lesions (brain metastasis/carcinomatous meningitis) Dehydration Infection (pneumonia, sepsis) Hyponatremia Anemia
	Others	Wernicke's encephalopathy (vitamin B_1 deficiency) Thyroid dysfunction Alcohol/nicotine withdrawal syndrome Paraneoplastic syndrome (encephalitis)
Precipitating factors		Uncomfortable physical symptoms (pain, dyspnea, fever, fecal impaction, urinary retention) Management requiring body movement restriction (continuous drip infusion, routes/drains, physical restriction) Sleep/awakening rhythm disturbance (management at night, frequent urination related to drip infusion) Sensory deprivation (vision/hearing impairment, darkness at night, unknown medical staff)
Predisposing factors		Advanced age (≥70 years) Organic lesions of the brain (cerebrovascular disorder, dementia)

2. Treatment of an etiological factor

Among etiological factors for delirium, drugs, hypercalcemia, infection, and dehydration may be managed/treated, and recovery may be achieved at a relatively high rate. On the other hand, the basic treatment is ineffective in many patients with organ failure related to cancer progression (respiratory failure, liver failure, renal failure) or intracranial lesions. That is, the possibility of recovery can be evaluated to some degree based on the presence or absence of organ failure as an etiological factor.

Drugs that may cause delirium include opioids, steroids, benzodiazepines, and anticholinergic drugs. If opioid dose-elevation for achieving the complete relief of pain without detailed assessment induces delirium, analgesic treatment other than opioid dose-elevation should be considered (see Chapter Pain). In the presence of delirium, patients sometimes complain of pain more strongly than when consciousness is clear. If there is no consistency regarding complaints on pain, or if the patient always affirms "pain" unclearly without answering the site of pain accurately to a question on pain, it may be necessary to reevaluate analgesic treatment.

Steroids are often used to control terminal-phase fatigue, but dose-elevation without sufficient assessment in the absence of a response may cause delirium. If there is no response to a steroid, the administration should be discontinued, or if the administration period is prolonged, the dose should be decreased to the extent not to cause symptom deterioration or adrenal failure. Concerning anticholinergic drugs, dose-reduction or discontinuation may help symptom palliation. With respect to benzodiazepines, which are used to sleep, if their involvement in delirium as a primary etiological factor is suspected, these drugs should be switched to an antipsychotic drug (e.g., quetiapine), sedative antidepressants (e.g., trazodone, mianserin), or hypnotics (e.g., orexin receptor antagonists, melatonin receptor agonists) which rarely cause delirium. If there is another etiological factor for delirium other than benzodiazepine in the terminal phase, discontinuation of a benzodiazepine may deteriorate insomnia. In such cases, benzodiazepine administration is often continued while combining it with an antipsychotic drug and decreasing its dose.

To treat hypercalcemia, bisphosphonates should be used. To treat infection, adequate antimicrobial drugs must be administered. In patients with dehydration, the

fluid infusion should be performed while confirming the absence of an increase in the pleural fluid or ascites.

The contents of such causal treatment depend on individual patients' goals of treatment. A decision should be made through discussion/consultation by multi-disciplinary staff as much as possible. For example, in patients in whom infection is considered to be an etiological factor and those with a limited life expectancy, no criteria for examinations to diagnose infection, the identification of causative bacteria, use of antimicrobial drugs, and drainage have been established; therefore, individualized evaluation is required.

Establishment of the goal of treatment

In patients with delirium related to organ damage or those with unfavorable general conditions, it is often difficult to achieve complete recovery from delirium. In impending death phase, clouding of consciousness is a part of the natural course toward death. In such cases, it is important to establish the goal of treatment individually in each patient.

Symptoms of delirium to be relieved should be clarified, and the goal of treatment should be established. Irritation/agitation, sleep disturbance at night, and hallucination/delusion are clinically problematic in many cases. To control these symptoms, the goal of treatment should be individually established: for example, irritation/agitation are reduced so that resting in bed may be maintained; sleep at night is targeted; visual hallucination, if it is not stressful for patients, may not be targeted.

As drugs with sedative actions are used for drug therapy for delirium, it is sometimes difficult to reconcile communication abilities, such as the patient's talk with his/her family, with symptom relief as the result of treatment. Therefore, the goal of treatment should be established while keeping a balance between the relief of symptoms (irritation/agitation, insomnia) and treatment-related demerits (inability to talk with the patient's family). In patients with difficult hyperactive delirium characterized by irritation/agitation, sleep disturbance at night, and hallucination/delusion, securing sleep at night is initially targeted, followed by the relief of irritation/agitation. Lastly, the

treatment of hallucination/delusion is targeted.

Alleviation of factors involved in delirium deterioration and care

1. Physical factors

Physical discomfort may deteriorate delirium in patients with advanced cancer. In addition to the management of pain or dyspnea, attention should be particularly paid to fever, fecal impaction, and urinary retention. To treat fever, the administration of an antipyretic or cooling should be performed. To control fecal impaction and urinary retention, the patients' gestures that suggest urination or fecal impaction should be carefully examined. Urinary retention should be confirmed using ultrasonography or by checking the unnatural protrusion of the lower abdomen in comparison with the pubic bone. Rectal examination confirms fecal impaction.

Treatment requiring body movement restriction is also an important factor that deteriorates delirium. Continuous drip infusion at night inhibits patient motions, promoting the appearance of delirium. Besides, sleep is affected due to frequent urination related to fluid infusion or venous route replacement. Therefore, if the fluid infusion is necessary, it should be performed during the daytime. It is also useful to minimize routes/drains.

2. Environmental/psychosocial factors

In the treatment of delirium, an environmental arrangement is important. In particular, it is suggested that the use of antipsychotic drugs for mild to moderate delirium shortens the prognosis without relieving symptoms. "Antipsychotic drug administration in the absence of environmental arrangement" is not adequate.

The goal of the environmental arrangement is to reduce/remove factors promoting the onset of delirium as potently as possible. For the management of sensory deprivation, sensory stimuli should be improved through friendly environmental stimuli

at an adequate level and the use of eyeglasses or hearing aids. For example, a dim light is put on at night to facilitate peripheral orientation, a calendar or clock is placed at a visible place so that the time sense may be maintained, and objects that have been used at home are placed to arrange a friendly environment. It is also useful to reassure the patient through frequent contact with the patient's family or familiar medical staff.

Medical treatment for delirium

1. Antipsychotic monotherapy

Initially, antipsychotic monotherapy should be performed for 1 to 3 days, and its efficacy should be evaluated.

a. Cases in which oral administration is possible

Low-dose quetiapine (10 to 50 mg/day) or risperidone (0.5 to 2.0 mg/day) is routinely used. If there is no adverse reaction in the process of dose-elevation, their doses may be increased to 100 to 200 mg/day and 3 to 5 mg/day, respectively. Olanzapine at 2.5 to 10 mg/day is also available.

b. Cases in which oral administration is impossible

The drip infusion or subcutaneous injection of haloperidol at 1.25 to 5 mg/day is most commonly used. This drug at 1.25 to 5 mg should be administered 1 to 3 times a day, and as an additional dose on agitation. There is no consensus for the further effects of haloperidol over 15 (to 20) mg/day; in clinical practice, such efficacy is rarely observed. As adverse reactions, extrapyramidal symptoms, such as akathisia and dystonia, which are extremely uncomfortable, appear 1 to 2 weeks after the start of administration in many cases; therefore, attention to adverse reactions should be continuously paid.

When sleep at night is preferentially targeted in the terminal phase, promethazine is combined with haloperidol in some cases. For example, haloperidol at 2.5 mg and

promethazine at 12.5 to 25 mg are intravenously infused or subcutaneously injected. These drugs exhibit sedative actions mediated by antihistaminic actions, facilitating falling asleep in comparison with a single administration of haloperidol. However, anticholinergic actions are simultaneously present, and they may cause delirium. Therefore, if possible, the administration period should be shortened. If administration deteriorates delirium, it should be discontinued.

If it is necessary to get enough sleep more accurately than co-administration of promethazine, benzodiazepines should be combined. As benzodiazepines may also deteriorate delirium, the administration period should be shortened if possible. If administration deteriorates delirium, it should be discontinued.

2. Pharmacological management when antipsychotic drugs are not effective

If there is no response to a firstly administered antipsychotic drug (insomnia, no alleviation of irritation/agitation), a drug that exhibits sedative effects through a different pharmacological action should be concomitantly used. That is, a benzodiazepine should be combined with an antipsychotic drug, or the latter should be switched to another antipsychotic drug with more potent sedative actions.

a. Cases in which oral administration is possible

If oral administration is possible, an antipsychotic drug should be changed or combined with another antipsychotic drug, or an antipsychotic drug should be combined with benzodiazepines, orexin receptor antagonists, or melatonin receptor agonists. Sedative antidepressants (trazodone, mianserin), which exhibit sedative effects and weak anticholinergic actions, are also used.

b. Cases in which oral administration is impossible

As the most frequent method, after establishing the dose of haloperidol as a minimum at which effects are obtained (for example, if there is no change despite dose-elevation (to 10 mg/day) after the partial effects of haloperidol at 2.5 mg/day are obtained, the dose should be decreased to 2.5 mg/day), benzodiazepines should be

concomitantly used as a drug that exhibits sedative effects through a different pharmacological action. Benzodiazepines should be intravenously infused or subcutaneously injected at night or specific intervals in the presence of marked symptoms of delirium during the daytime so that patients may get enough sleep. In many patients with delirium, the intermittent administration of benzodiazepines in addition to a specific dose of haloperidol facilitates sleep at night, relieving irritation/agitation during the daytime. However, if delirium after awakening is repeated despite sleep through the drip infusion of these drugs, continuous sedation should be considered.

As other options, the drip infusion of chlorpromazine can be selected. The anticholinergic actions of this drug are more potent than those of haloperidol; therefore, the use of this drug for the treatment of delirium is less frequent than that of haloperidol. However, chlorpromazine exhibits sedative effects, and it is used when there is no sufficient response to haloperidol, or when treatment with haloperidol is difficult due to extrapyramidal symptoms as adverse reactions. In such cases, chlorpromazine administration should be started at a low dose (5 to 10 mg/day).

Drugs that can be injected include levomepromazine. This drug exhibits potent anticholinergic actions and may deteriorate delirium or decrease blood pressure. However, it is sometimes used as a drug for delirium or a sedative.

Dyspnea

Outline (Table 1)

In addition to delirium, dyspnea accounts for the greater portion of refractory symptoms. From the viewpoint of refractory symptoms, it refers to dyspnea at rest (not dyspnea on movement). In many cases, hypoxemia is observed.

Treatment following some etiological factors for dyspnea may be the most effective method that contributes to dyspnea relief. Therefore, it is necessary to evaluate the etiology of dyspnea. Relatively frequent etiological factors include enlargement of primary/metastatic lung tumors, carcinomatous lymphangiomatosis, pleural effusion, pneumonia, ascites- or hepatomegaly-related diaphragmatic movement limitation, and heart failure. Other etiological factors include stenosis of the airway, superior vena cava syndrome, pericardial fluid, pulmonary embolism, phrenic nerve paralysis, pneumothorax, anemia, metabolic acidosis, and pleural dissemination-/thoracic wall infiltration-related movement restriction of the thorax. Furthermore, dyspnea associated with systemic-weakness-related fatigue of the respiratory muscle may occur even when there is no local etiology in the chest. In many patients with advanced cancer, several etiological factors contribute to dyspnea. Etiological factors can be often evaluated based on medical history, previous imaging findings, and physical findings. However, examinations to identify an etiology should be considered following patients' wishes or conditions.

Dyspnea in terminally ill patients is complicated by hypoxemia as a type of organ failure in many cases, making complete symptom relief difficult. The goal of treatment should be established for individual patients, considering the balance between maintenance of consciousness or communication and symptom relief. Concerning care, non-pharmacological management, such as wind application to the face and comfortable posture arrangement, should be performed. For pharmacological management, opioids are primarily used. If oral administration is impossible, they may be administered by continuous subcutaneous infusion. Low-dose opioids are effective in many cases, but, if

their effects are insufficient, the following options may be selected: 1) the dose of an opioid is increased within a permissible range at which there may be no adverse reaction, 2) an opioid is switched to another opioid, and 3) low-dose midazolam is combined with an opioid. In any case, the dose should be titrated so that the goal established with the patient may be achieved following distress.

The contents to be reviewed in patients with difficult dyspnea are shown in Table 2, although all are not listed.

Table 1 Outline of dyspnea treatment

	Points	Management cases
Identification of an etiological factor and treatment	Identification of an etiological factor	The etiology of dyspnea should be clarified based on medical history, previous imaging findings, and physical findings.
	Treatment for etiological factors that can be treated	Pleural effusion, ascites, heart failure, stenosis of the airway, superior vena cava syndrome, and pericardial fluid.
Establishment of the goal of treatment	The goal of treatment should be established.	The realistic goal of treatment should be established with the patient by sharing the fact that it is sometimes difficult to achieve the complete relief of distress at the terminal phase. The balance between the level of consciousness or communication and symptom relief should be considered.
Alleviation of factors involved in distress deterioration and care	Care for physical factors	Dyspnea-relieving postures should be arranged, and environmental adjustment (room temperature/airflow) should be promoted. Reduction of excessive fluid infusion should be considered.
	Care for psychosocial factors	Psychosocial support, especially the management of anxiety, should be performed. Sleep at night should be secured.
Medical treatment	Pharmacological management	An opioid should be continuously administered. It should be combined with an anxiolytic drug (including midazolam).
	Treatment other than pharmacological management	Oxygen should be administered to treat hypoxemia.

Table 2. Contents to be reviewed in patients with difficult dyspnea

Identification of an etiological factor and treatment

-Etiological factors should be estimated, and the etiological factors that can be treated should be reviewed.

-Attention should be paid to etiological factors of which the outcome may depend on treatment, such as pleural effusion, ascites, heart failure, stenosis of the airway, superior vena cava syndrome, and pericardial fluid.

-Steroid therapy should be considered in patients with enlargement of primary/metastatic lung tumors, carcinomatous lymphangiomatosis, stenosis of the airway, or superior vena cava syndrome.

Establishment of the goal of treatment

-A realistic goal should be established with the patient, sharing the difficulty of targeting the complete relief of dyspnea.

-If the relief of dyspnea is not compatible with the maintenance of consciousness or communication, the physician should consult the patient concerning the patient's priority.

Alleviation of factors involved in distress deterioration and care

-Dyspnea-relieving postures should be arranged, and environmental adjustment (slightly low room temperature, airflow to the face) should be performed.

-If the fluid infusion is excessively provided, volume-reduction should be considered.

-Psychosocial support, especially the management of anxiety, should be performed.

-Sleep at night should be secured.

Medical treatment

-Opioids (primarily, morphine) should be used. If oral administration is impossible, they may be administered by continuous subcutaneous infusion.

-When adding the continuous infusion of morphine in patients receiving high-dose fentanyl patches for analgesia, it should be considered that the 1-hour volume of continuously infused morphine as an additional dose may be insufficient as the dose of a rescue dose on dyspnea. In contrast, if a rescue dose is established based on the total dosage of fentanyl patches and morphine as an additional dose, it may be too high; therefore, caution is needed.

-If the effects of low-dose opioids are insufficient, the following options may be selected: 1) the dose of an opioid is further increased within a permissible range at which there may be no drowsiness, 2) an opioid is switched to another opioid, and 3) morphine is combined with a low-dose benzodiazepine anxiolytic drug (midazolam) to relieve symptoms.

-If opioid-related neurotoxicity (delirium, myoclonus) is observed, the dose of an opioid should not be increased.

-If hypoxemia is present, oxygen should be administered.

Identification of an etiological factor and treatment

1. Identification of an etiological factor

Dyspnea is a relatively frequent symptom in advanced cancer patients. From the viewpoint of a refractory symptom, it refers to dyspnea at rest, and it is complicated by hypoxemia in many cases. Treatment following some etiological factors for dyspnea may be the most effective method that contributes to dyspnea relief. That is, to regard dyspnea as refractory, it is necessary to evaluate the etiology of dyspnea (Table 3).

Etiological factors are classified into those directly related to cancer and those that are not related to cancer, and into intra- and extra-thoracic factors (Table 3). Besides, even if there is no local intra- or extra-thoracic lesion, systemic-weakness-related fatigue of the respiratory muscle may induce dyspnea. In particular, several etiological factors often causes dyspnea in terminal cancer patients.

The etiology of dyspnea can be evaluated based on medical history, previous imaging findings, and physical findings on dyspnea. For example, etiological factors, such as enlargement of primary/metastatic lung tumors and carcinomatous lymphangiomatosis, can be estimated from previous imaging findings and gradually progressing dyspnea, even though there is a possibility that other factors may be present. In the presence of pleural effusion, the reduction/loss of unilateral respiratory sounds are detected on auscultation, and a definitive diagnosis can be made using ultrasonography. Pneumonia can be evaluated based on symptoms, such as an infection-related increase in the sputum volume and fever, auscultation findings, and hematological data. Ascites-/hepatomegaly-related compression can be confirmed by palpating ascites or a swollen liver on physical examination. Heart failure can be evaluated based on a history of heart failure, auscultation findings (crackles), imaging findings suggestive of cardiac hypertrophy, and the deterioration of edema. Stenosis of the airway can be evaluated based on the presence of a lesion that may induce stenosis on previous imaging and deterioration of stenotic sounds. Superior vena cava syndrome can be evaluated based on the presence of a lesion that may compress the superior vena cava on previous imaging and deterioration of upper limb/facial edema. Pericardial fluid

Table 3 Primary etiological factors for dyspnea in cancer patients and etiology-based treatment

	Etiological factor	Etiology-based treatment
Relatively frequent etiological factors	Enlargement of primary/metastatic lung tumors	Steroids
	Carcinomatous lymphangiomatosis	Steroids
	Pleural effusion	Drainage of pleural effusion
	Pneumonia	Antimicrobial drug administration
	Ascites-related diaphragmatic movement limitation	Drainage of ascites
	Hepatomegaly-related diaphragmatic movement limitation	
	Heart failure	Treatment of heart failure (such as diuretics)
	Systemic weakness-related fatigue of the respiratory muscle	
Others	Stenosis of the airway (trachea/bronchus)	Steroids, Stenting, radiotherapy
	Superior vena cava syndrome	Steroids, Stenting, radiotherapy
	Pericardial fluid	Drainage of pericardial fluid
	Pulmonary embolism	Anticoagulant therapy
	Phrenic nerve paralysis	
	Pneumothorax	Intrathoracic deaeration
	Anemia	Erythrocyte transfusion
	Metabolic acidosis	
	Pleural dissemination-/thoracic wall infiltration-related movement disturbance of the thorax	
	Exacerbation of underlying respiratory diseases (COPD, bronchial asthma)	Bronchodilators

is identified based on medical history or imaging findings in some cases, but a definitive diagnosis should be made using echocardiography if there is no other etiological factor. Pulmonary embolism should be suspected if rapid dyspnea and hypoxemia occur. Bilateral phrenic nerve paralysis is related to transverse palsy of the cervical spinal cord, but its incidence is low. In the presence of pneumothorax, the reduction/loss of unilateral respiratory sounds are detected on auscultation, and pneumothorax can be definitively diagnosed using imaging procedures. Anemia is definitively diagnosed based on hematological data. Dyspnea related to metabolic acidosis essentially refers to tachypnea (an increase in respiratory movement requirement) associated with renal-failure-related acidosis compensation. Pleural dissemination-/thoracic wall infiltration-related movement restriction of the thorax is diagnosed based on previous imaging and visual inspection findings.

Thus, the etiology of dyspnea can be estimated to some degree based on the clinical course, but it is often difficult to evaluate whether a new condition of dyspnea occurred during the clinical course (e.g., carcinomatous lymphangiomatosis may have deteriorated, but the volume of pleural effusion may also have increased). The extent of etiology investigation should be reviewed, considering the following points: the presence of treatment for the estimated etiology of dyspnea, patient wishes, and examination/treatment tolerability of the general condition.

2. Treatment for etiological factors

There are etiology-based treatments for some factors for dyspnea (Table 3). Of course, if the effects of anticancer treatment are expected, its indication should be examined. The invasiveness of treatment varies among patients, and the extent of causal treatment depends on the goal of treatment in individual patients. The expected merits of treatment (a sufficient time to obtain therapeutic effects, treatment tolerability) should be sufficiently considered following the prognosis or general condition after understanding the patient's wishes through multidisciplinary discussion as much as possible.

After performing treatment for respective etiological factors, whether the expected effects of treatment were obtained should be sufficiently assessed, and, if there is no

response, continuing the treatment without a reconsideration of medical indication must be avoided.

Minimally invasive, effective treatments include steroid therapy for enlargement of primary/metastatic tumors, carcinomatous lymphangiomatosis, stenosis of the airway, and superior vena cava syndrome, drainage of pleural effusion, drainage of ascites, and diuretics for heart failure. To patients with difficult dyspnea, steroids at a moderate or high dose should be administered, and their effects should be confirmed (e.g., betamethasone at 4 to 8 mg/day is administered for 3 to 7 days, and its effects are evaluated). Steroids may induce adverse events such as delirium; therefore, if there is no response, the dose should be decreased, or the administration should be discontinued. In the case of long-term administration of steroids, the dose should be carefully and gradually decreased to the extent not to cause symptom deterioration or adrenal failure.

Establishment of the goal of treatment

In the presence of hypoxemia, it is difficult to achieve the complete relief of dyspnea especially when the patient move in many cases. It is important to share the goal of palliative care with patients. The administration of drugs, such as opioids and benzodiazepines, may induce drowsiness regardless of the physicians' intention, and relief of distress with these drugs is not compatible with thinking or communication abilities in some cases. Some patients wish the relief of dyspnea should be prioritized even if drowsiness is increased, but others wish clear consciousness without drowsiness should be prioritized even if dyspnea is present. It is important to individually discuss the goal of treatment regarding the permissible range of drowsiness and priority with patients. For example, "wish to sleep well without feeling dyspnea at night, but stay up to talk despite mild dyspnea during the daytime" or "drowsiness can be tolerable if dyspnea is relieved".

In particular, drowsiness is not always induced by drugs (opioids, benzodiazepines) in the terminal phase, and it may reflect a reduction in consciousness related to the natural course before death. Health care professionals should establish the goal of treatment while recognizing the patient's clinical phase.

Alleviation of factors involved in dyspnea deterioration and care

1. Physical factors

Posture should be arranged so that patients may not feel dyspnea. Patients may not feel dyspnea in a lateral position rather than a supine position, and many patients prefer slight head elevation (a sitting position).

Patients with dyspnea tend to feel less dyspnea at low room temperature. A temperature that the caregiver feels a little cold may relieve dyspnea, although it depends on patients' preference. Furthermore, dyspnea may be relieved by applying airflow to the face using an electric fan or circulating room air.

Dyspnea deteriorates when patients move. An environmental arrangement should be performed so that the patient's movement concerning activities of daily living may be minimized. If possible, respiration methods, such as abdominal breathing, pursed lips breathing, and manual respiratory assistance should be arranged.

An excessive fluid infusion may increase sputum or airway secretion or deteriorate dyspnea through pulmonary edema or pleural effusion. Therefore, the fluid volume should be decreased. When continuous drip infusion is performed to secure an intravenous route for continuous opioid administration, the fluid volume can be decreased by switching this procedure to continuous subcutaneous infusion.

2 Psychosocial factors

Anxiety is closely associated with dyspnea. When anxiety worsens, dyspnea deteriorates, and dyspnea itself further deteriorates anxiety. Psychosocial support, especially management to reduce anxiety, should be conducted. If the involvement of anxiety rather than physical factors in the development/enhancement of dyspnea is suggested, the administration of an anxiolytic drug for anxiety relief should be considered.

Furthermore, it is important to maintain sleep at night, when anxiety may be enhanced.

Medical treatment for dyspnea

1. Pharmacological management

For the relief of dyspnea, opioids, including morphine, and benzodiazepine anxiolytic drugs are primarily used. Concerning pharmacological management for dyspnea, the border between “standard palliative care” and “palliative sedation” is vague based on the finding that a sedative, midazolam, may be effective for dyspnea. Administration of midazolam for pain is not common, but the continuous administration of low-dose midazolam, not for reducing consciousness, but for dyspnea relief, may be probable.

a. Start of opioid therapy for dyspnea

For pharmacological management for dyspnea, morphine is used as a standard drug. Several clinical trials and meta-analyses have demonstrated its efficacy. Concerning opioids other than morphine, there is little evidence, but oxycodone may exhibit constant effects based on clinical experience and pharmacological actions. Fentanyl is not commonly used.

Concerning the administration route, opioids should be orally administered if possible. However, in many patients with difficult dyspnea to be covered by the present guidelines, the general condition is unfavorable, making oral administration impossible. Therefore, continuous subcutaneous infusion is primarily adopted. If a venous route is present, continuous intravenous infusion may be performed, but the fluid volume tends to become large to keep intravenous route. A large fluid volume may contribute to the deterioration of pleural effusion or pulmonary edema; therefore, continuous subcutaneous infusion is more ideal as an administration route.

Thus, for opioid therapy for dyspnea, the continuous subcutaneous infusion of morphine is primarily selected.

1) Management of opioid-naive patients

When starting opioid therapy for dyspnea in opioid-naive patients, morphine should be selected as a basic choice. Oxycodone is sometimes selected, considering the

patient's condition such as renal dysfunction. Opioid therapy should be started at a dose lower than that used for pain control. Concretely, the initial doses of morphine for continuous subcutaneous infusion should be 6 to 12 mg/day.

2) Management of opioid-tolerant patients

In patients who have been treated with opioids to relieve pain, management depends on the type of opioid.

In those to whom morphine has been regularly administered for pain control, its dose should be increased by approximately 25 to 50%.

In those in whom fentanyl patches have been used for pain control, they should be switched to morphine basically. However, in many patients receiving fentanyl patches at a middle dose or higher (e.g., ≥50 μg/hour), partial (1/3 to 1/2) switching to morphine can be adopted to avoid changes in the general condition related to complete switching to morphine. After partial switching, the effects/adverse reactions should be evaluated, and a change of the remainder to morphine should be considered if necessary.

In some cases, the continuous subcutaneous infusion of morphine is added to fentanyl patches which are continued with the same dose. This is because a change of an opioid to another opioid may influence the status in patients with a frail general condition such as the rapid progression of dyspnea. When morphine is used with fentanyl patches, morphine is subcutaneously injected as a rescue drug at the time of dyspnea deterioration. The dose of a rescue drug should be calculated from the total opioid dose involving the dose of fentanyl patches; attention should be paid so that the rescue dose may not be over- or underestimated.

b. Management in cases in which low-dose morphine are ineffective for dyspnea

If low-dose morphine is effective, its dose should be continuously adopted. There is no criterion for the utmost of increase in the dose of morphine in non-responders to low-dose morphine. Basically, their doses should be increased step by step until patients express morphine as "effective for dyspnea" and to a dose at which dyspnea can be relived in the absence of drowsiness, as described for opioid therapy for pain. If dyspnea is relieved, the dose should be maintained.

If there is no sufficient response despite step-by-step morphine dose-elevation, one

of the following 3 treatment options should be selected: 1) the doses of morphine should be further increased in the range of “no adverse reaction”, 2) an opioid should be changed, and 3) a benzodiazepine anxiolytic drug (parenteral administration: midazolam) should be combined with morphine, considering opioids ineffective.

1) Opioid dose-elevation

The adequacy of further increasing the dose of morphine should be comprehensively evaluated from the following viewpoints: whether the effects of dose-elevation can be confirmed, and whether opioid-related neurotoxicity (drowsiness, delirium) or respiratory suppression is present.

If neurotoxicity, such as delirium, is observed during morphine dose-elevation, further dose-elevation is not adequate. If the dose of an opioid is increased in the presence of neurotoxicity, relief of distress may not be achieved, leading to the deterioration of overdosage-related respiratory suppression or neurotoxicity/oversensitive symptoms (myoclonus, opioid-induced hyperpathia, convulsion). This is one of the reasons why morphine dose-elevation for the purpose of sedation is not recommended in palliative sedation guidelines in many countries. In this case, the dose of an opioid should be decreased, and treatment for delirium should be simultaneously performed (See Chapter Delirium).

2) Opioid switching

If patients receiving oxycodone for dyspnea do not respond to dose-elevation, switching to morphine should be considered.

3) Combination therapy with benzodiazepine anxiolytic drugs

When administering benzodiazepine anxiolytic drugs alone to patients with dyspnea, anxiety, as a dyspnea-exacerbating factor, is targeted. Actually, the results of previous clinical studies have not demonstrated the efficacy of monotherapy with benzodiazepines for dyspnea.

On the other hand, several studies suggested that the combination of an opioid and benzodiazepine relieves dyspnea in cancer patients. In clinical practice, a low-dose

benzodiazepine is often combined with an opioid. Concretely, if oral administration is possible, lorazepam or alprazolam is used. If oral administration is impossible, midazolam is primarily used.

When combining midazolam, as a benzodiazepine anxiolytic drug, with an opioid to relieve dyspnea, the administration of midazolam should be started at 2.5 to 5 mg/day, at which drowsiness may not be enhanced, and the dose should be regulated in accordance with the degree of symptom. However, benzodiazepine anxiolytic drugs exhibit sedative actions, and may reduce consciousness at a high dose. In particular, midazolam at >10 mg/day exhibits potent sedative actions, and it may be difficult to achieve the relief of dyspnea while maintaining consciousness; therefore, its dose generally should be established as ≤10 mg/day.

2. Treatment other than pharmacological management

If hypoxemia is present, oxygen should be administered.

On the other hand, oxygen is not always effective in the absence of hypoxemia, but it may be administered to evaluate its effects in patients with difficult dyspnea in whom there is no other effective method. In this case, administration should be continued if the effects are clear, but the discontinuation of oxygen administration should be considered if the effects are unclear or if adverse events (e.g., discomfort associated with oxygen tube-related restriction, restriction-related deterioration of delirium) are observed.

Pain

Outline (Table 1)

It is not so common that pain becomes refractory and requires palliative sedation. However, it may occur even in patients with favorable general conditions, differing from dyspnea and delirium, which reflect organ damage. It may become difficult to relieve pain in some patients in whom oral intake is possible. If palliative sedation is performed in patients with favorable general conditions, their general conditions may be markedly influenced, or the prognosis may be shortened. Therefore, if considering palliative sedation for pain, it must be carefully examined that pain is truly refractory, that is, whether there is no method to relieve pain other than palliative sedation.

Firstly, it is necessary to accurately evaluate the pathogenesis of difficult pain. If health care professionals increase the doses of opioids based on the incorrect hypothesis that pain may be always caused by cancer in patients with cancer, there may be no analgesic effects, and the concomitant development of delirium or cognitive disorder may further make pain assessment difficult. It is important to clarify the etiology of pain based on pain history and physical examination/imaging findings. If its etiology can be identified, treatment for the etiology of pain (e.g., anticancer treatment, antimicrobial drug administration for infectious diseases) may help pain palliation. If pain exacerbates after increasing the dose of an opioid, the possibility of opioid-related hyperalgesia should be considered. To control chronic non-cancer pain, e.g., low back pain, intervention by analgesic drugs other than opioids, care for psychosocial factors, nerve block, and rehabilitation should be prioritized.

If pain is considered to become difficult to be palliated based on an identified etiology (e.g., neuropathic pain related to cancer involving the nerves, incidental bone pain), the physician should talk with the patient about the goal of treatment, assuming that it may be impossible to achieve the complete relief of pain. After explaining the pathogenesis of pain, the goal of treatment should be established by sharing treatment methods that may become options (e.g., nerve block). If pain relief is not compatible

with the maintenance of consciousness or communication, a treatment option should be chosen, considering the patient's priority.

Table 1 Outline of pain treatment

	Points	Management cases
Identification of an etiological factor and treatment	Identification of an etiological factor	The etiology of pain should be clarified through an pain history, confirmation of the site of pain, physical examination of desensitization by palpation, and confirmation of imaging findings.
	Treatment for etiological factors of pain that can be treated	Treatment for the etiology of pain, such as anticancer or infectious disease treatment.
	Examination of the possibility of hyperalgesia related to opioids	Dose-reduction or switching of opioids.
	Treatment for non-cancer pain	Analgesic drugs other than opioids, care for psychosocial factors, nerve block, and rehabilitation.
Establishment of the goal of treatment	The goal of treatment should be established based on the pathogenesis of pain.	The pathogenesis of pain should be explained to patients so that they can understand it, and the realistic goal of treatment should be established. The balance between the level of consciousness or communication and symptom relief should be considered.
Alleviation of factors involved in distress deterioration and care	Care for physical factors	Pain-relieving movements/postures. Environmental adjustment (e.g., use of a mat) or brace utilization.
	Care for psychosocial factors	Care for relieving anxiety, fears, anger, sense of isolation, and depression.
Medical treatment	Pharmacological management	For persistent pain, the dose of an around-the-clock opioid should be increased in an effective range in which there is no influence on consciousness. Control of breakthrough pain. If the effect of an opioid is insufficient, the administration route or type of opioid should be changed, or the opioid should be combined with an adjuvant analgesic drug.
	Treatment other than pharmacological management	Radiotherapy. Nerve block.

In the treatment of cancer pain, factors that deteriorate pain should be removed (e.g., environmental adjustment to facilitate daily activities through movement without pain), and psychosocial support should be sufficiently conducted. As pharmacological management for cancer pain, the doses of around-the-clock opioids, which are effective for persistent pain should be increased in a range in which there is no influence on consciousness. If breakthrough pain is present, it should be controlled using fast-acting analgesics. If an opioid is ineffective, the administration route or opioid type should be changed, and/or the opioid should be combined with adjuvant analgesics. In addition to pharmacological management, radiotherapy or nerve block should be considered.

The contents to be reviewed in patients with difficult pain are shown in Table 2, although all are not listed.

Identification of an etiological factor and treatment

It is necessary to evaluate the etiology of pain and plan etiology-based analgesic methods. If the dose of an opioid is increased due to the presence of pain alone, no effect may be obtained, and psychiatric symptoms such as delirium may occur, making pain treatment difficult.

The etiology of pain can be clarified based on imaging findings, pain history (site of pain, features of pain, movement-related pain), and physical examination findings (e.g., dysesthesia at the site of pain) in most cases. In an environment where no imaging procedure can be performed, the pathogenesis of pain should be clarified as accurately as possible through taking pain history and physical examination.

1. Differentiation of cancer pain from non-cancer pain

All of the pain in patients with cancer are not related to cancer: disuse-related muscle-skeletal pain, cancer-treatment-associated pain (e.g., delayed postoperative pain, chemotherapy-induced peripheral neuropathy, late effects of radiation therapy), and chronic non-cancer pain (e.g., chronic low back pain, osteoarthrosis, shoulder periarthritis, muscle contraction headache).

Table 2. The contents to be reviewed in patients with difficult pain

Identification of an etiological factor and treatment

-The pathogenesis of pain should be evaluated as accurately as possible.

-Treatment for the etiology of pain, e.g., anticancer or infectious disease treatment.

-The possibility of opioid-related hyperalgesia should be considered.

-Cancer pain should be differentiated from non-cancer pain (e.g., chronic low back pain).

-For disuse-related muscle-skeletal pain, posture/mat arrangement, physical therapy (relieving the tension of the muscles), and trigger point injection should be performed.

Establishment of the goal of treatment

-A realistic goal should be established, sharing the recognition that complete pain relief cannot be targeted with the patient.

-If the complete pain relief is not compatible with the maintenance of consciousness or communication, treatment should be performed, considering the patient's priority.

Alleviation of factors involved in pain deterioration and care

-Pain-relieving movements/postures should be arranged, and environmental adjustment (the use of an electric bed or mat) or brace utilization should be promoted.

-Care for relieving anxiety, fears, anger, a sense of isolation, and depression should be provided.

Medical treatment: Pharmacological management

-For persistent pain, the dose of an around-the-clock opioid should be increased in an effective range in which there is no influence on consciousness. If a precise response is not obtained in the process of dose-elevation, or if delirium/mild consciousness disturbance is suspected, whether further opioid dose-elevation is adequate must be reassessed.

-A fast-acting analgesic drug at a dose at which it is effective for breakthrough pain should be prepared (e.g., environmental arrangement for prompt dosing at the onset of pain, explanation to the patient, sufficient dose at which analgesic effects are obtained, adequate administration interval).

-The administration route of an opioid should be changed (oral/transdermal administration should be switched to continuous subcutaneous/intravenous administration).

-The type of opioid should be changed.

-An adjuvant analgesic drug at a sufficient dose should be used. If monotherapy is ineffective, the drug should be switched to another adjuvant analgesic drug, or combination therapy with adjuvant analgesic drugs that have different action mechanisms should be considered while paying attention to adverse reactions.

Medical treatment: Treatment other than drug therapy

-Radiotherapy should be considered.

-If pain is localized, nerve block (e.g., epidural block) should be considered.

-Intrathecal analgesia (e.g., intrathecal morphine) should be considered.

It should be examined pain other than cancer pain is involved in current difficult pain.

If disuse-related muscle-skeletal pain is present, posture/mat arrangement, physical therapy (relieving the tension of the muscles), and trigger point injection rather than analgesia with opioids should be considered. The oral administration or external application of non-opioid analgesic drugs are useful in some cases.

Chronic non-cancer pain or cancer-treatment-related pain, such as delayed postoperative pain, is difficult to relief completely in many cases. The goal of treatment is to maintain activities of daily living (ADL) by introducing nerve block, psychosocial support, and rehabilitation in addition to therapy with analgesic drugs other than opioids, but not complete pain relief. That is, for these types of pain, opioid therapy following the WHO analgesic ladder for cancer pain is not indicated, and it is not the first option to relieve pain. Such non-cancer pain may deteriorate due to a muscle-weakness and reduction in ADL or an increase in psychosocial problems in the terminal phase of cancer. In such cases, support for psychosocial factors should be intensified, and, if the pain is not relieved, low- to middle-dose opioid therapy should be considered in patients with a life expectancy of ≤ 2 to 3 months.

2. Pain that tends to become difficult

Factors for difficult pain control include young age, neuropathic pain, breakthrough pain, psychosocial factors (mental distress), previous high-dose opioid exposure, and cognitive impairment.

With respect to the pathogenesis of pain, pain related to tumor-related compression/infiltration of the nerve plexus or spinal cord (e.g., spinal cord infiltration, brachial plexus infiltration of Pancoast tumors, sacral plexus infiltration of intra-pelvic tumors), pancreatic cancer pain, pain related to extensive pleural dissemination, pain related to multiple bone metastases (especially those with marked osteolytic changes), and perineal pain tend to become difficult (Table 3). In many cases, it is impossible to achieve the complete relief of pain by high-dose opioid therapy alone. If the dose of an analgesic drug is increased until the complete relief of pain, psychiatric symptoms related to relative overdose administration may appear. In particular, delirium may

develop in terminally ill cancer patients. If it appears, cognitive impairment may further make pain treatment difficult. For these types of difficult pain, it should be examined that other analgesic methods are sufficiently performed.

Table 3. Cancer pain that tends to become difficult

-Spinal cord infiltration -Brachial plexus infiltration of Pancoast tumors -Sacral plexus infiltration of intra-pelvic tumors -Pancreatic cancer pain -Thoracic pain related to extensive pleural dissemination -Multiple bone metastasis-related pain with movement (especially those with marked osteolytic changes) -Perineal pain

3. Treatment for an etiological factor

If cancer is an etiological factor for pain, anticancer therapy should be examined. If the concomitant development of an infectious disease deteriorates pain, infectious disease treatment should be considered. In patients with intestinal obstruction, pain may be relieved by gastrostomy, colostomy, bypass operation due to decompression around the site of stenosis/obstruction, or endoscopic stenting due to the improvement of passage. In patients with cholecystitis or appendicitis, the use of antimicrobial drugs or surgery should be considered. The physician should consult an orthopedist to ask surgical therapy may be indicated for pain related to deformity of the shoulder joint or articulation coxae.

In any case, the general condition, expected prognosis, patient's or family's wishes, and treatment-related merits/demerits should be comprehensively examined.

Establishment of the goal of treatment

It is important for the physician to share the goal of analgesia with the patient on the assumption that difficult pain may be present. In some cases, pain relief is not compatible with the maintenance of consciousness or communication. Whether pain relief is prioritized despite marked drowsiness or whether clear consciousness is prioritized despite the incomplete relief of pain depends on the values of individual patients. Many patients wish to establish goals such as they can sleep at night even if the pain does not completely relief throughout the day and pain sometimes occurs during the daytime, but it subsides when an additional analgesic drug is used a few times a day".

When establishing the goal of treatment, the etiology of pain should be explained precisely. The pathogenesis of pain should be explained so that the patient can understand it (e.g., a recurrent tumor involves nerves of the hands and legs, causing pain). This makes it possible to share the reason why pain is difficult to relief completely and establish the goal of pain treatment with the patient. After the explanation, many patients may feel relieved through the understanding of the detailed mechanism of difficult pain, even if some levels of pain persists. Explaining the etiology of pain precisely may contribute to the relief of a portion of mental distress as a factor that makes pain relief difficult. Even if mild pain persists, health care professionals should continuously support patients at maximum using various methods and tell them that they will not be abandoned.

Alleviation of factors involved in pain deterioration and care

1. Physical factors

Lifestyle arrangements or environmental adjustments should be conducted so that pain may be relieved.

For example, in patients with bone metastasis, the affected site should be protected,

and bone deformity should be relieved. To relieve severe fracture-related pain, a brace should be used. The state of bone metastasis should be evaluated in consultation with Orthopedists. In particular, dynamic strength assessment and neurological diagnosis are necessary. Persistent pain that is related to bone metastasis is often relieved by around-the-clock analgesics, whereas pain with movement is difficult to control by around-the-clock opioids alone despite the preventive use of a rescue dose. Therefore, it is necessary to arrange pain-relieving motions, establish an environment to avoid pain-enhancing motions, and adjust brace utilization methods by introducing rehabilitation by physical/occupational therapists so that pain may be relieved by these methods in combination with pharmacological management.

2. Psychosocial factors

In cancer patients, psychosocial factors are often involved in difficult pain. Furthermore, the presence of psychological distress is a factor that makes pain control difficult. Psychosocial factors should be examined by a multi-disciplinary team consisting of a nurse, social worker, psychiatrist, and psychologist.

In patients with a long history of pain, pain is repeatedly recognized, and overestimation of pain makes them distressed (catastrophic thinking of pain), inducing unfavorable emotions, such as anxiety, fear, anger, loneliness, and depression, and modifying the recognition of pain (pain deteriorates). Such an unfavorable circulation chronically aggravates pain. Therefore, if anxiety, fear, anger, loneliness, and depression can be reduced through assessment from various aspects including psychosocial factors in addition to the patient's physical factors, pain may be relieved.

In particular, opioids prescribed for rescue dose of pain are sometimes used to relieve mental problems (e.g., anxiety, irritation) or physical symptoms (e.g., insomnia, fatigue) other than pain. In such cases, it is necessary to sufficiently assess reasons for opioid usage other than pain, that is, mental problems or physical symptoms other than pain, and perform strategies to control them.

Medical treatment for cancer pain

1. Pharmacological management

Non-opioids, opioids, and adjuvant analgesics should be properly combined for adequate pain management. It is important to differentiate breakthrough pain from persistent pain.

a. Dose-elevation of opioids

The around-the-clock administration of opioids is effective for persistent pain. In many cases, analgesic effects are obtained by increasing the dose of an opioid following the deterioration of pain. If consciousness is clear, there is no upper limit of the doses of opioids within a range in which patients can answer the effectiveness of dose-elevation clearly.

On the other hand, when the dose of an opioid is increased, its use is often restricted due to dose-limiting toxicities. In particular, the doses of opioids are restricted in the presence of central nervous symptoms such as drowsiness, consciousness disturbance, and delirium. If patients without consciousness disturbance become unable to answer the site or severity of pain precisely in the process of opioid dose-elevation, the onset of delirium or mild consciousness disturbance should be suspected. If the dose of an opioid is further increased despite insufficient pain assessment, pain after dose-elevation cannot be evaluated, increasing the risk of delirium. The dose of an opioid may be increased in the permissible range of drowsiness, but it is important to reassess whether further opioid dose-elevation is appropriate from the following viewpoints: the dose is increased based on the patient's wishes, the analgesic effect of an opioid is enhanced with an increase in the dose, and dose-limiting toxicities (delirium, myoclonus) is present.

If opioid-induced delirium appears, dose-elevation should be avoided, or the dose should be carefully decreased. Besides, the administration route or type of opioid should be changed, or the opioid should be combined with an adjuvant analgesic. When an opioid is considered to be effective for pain despite the possibility that it may deteriorate delirium, opioid dose-elevation and delirium treatment with antipsychotic

drugs may be simultaneously performed in some cases.

If the patient increasingly complains of pain despite dose-elevation, the possibility of opioid-induced hyperalgesia (OIH) should be considered. In this case, it is necessary to evaluate whether the pain is relieved by decreasing the dose or opioid switching.

b. Change of the administration route of opioids

If sufficient analgesic effects are not obtained by oral or transdermal opioid administration, the opioid should be administered via intravenous or subcutaneous routes. For example, a method of switching the oral administration of morphine to continuous subcutaneous administration is adopted.

c. Opioid switching

If sufficient effects are not obtained despite a sufficient increase in the dose of an opioid, the type of opioid should be changed. Under some circumstances, two strong opioids may be simultaneously used. In particular, when a favorable balance between the improvement of analgesic effects and the relief of adverse reactions is achieved in the process of switching a portion of a massive-dose opioid to another opioid, two opioids are continuously used in some cases. For example, if fentanyl patches are ineffective, switching its portion to the continuous subcutaneous injection of morphine may be effective.

Methadone is an opioid that has an action mechanism on both μ-opioid receptors and NMDA receptors, and pain may be relieved through a change from opioids that primarily act on μ-opioid receptors (morphine, oxycodone, fentanyl) in patients with neuropathic pain.

d. Use of adjuvant analgesic drugs

Neuropathic pain accounts for approximately one-third of refractory pain, and it is impossible to relieve pain using opioids alone in many cases. Although there are many types of adjuvant analgesic drugs, it remains to be clarified which drug is the most effective concering the type of pain. Therefore, if the effects of a single adjuvant analgesic drug are not sufficient, another adjuvant analgesic drug with a different action mechanism should be administered to evaluate its efficacy. To evaluate the

ineffectiveness of an adjuvant analgesic drug, it is necessary to increase its dose to a maximum in the permissible range of adverse reactions (e.g., drowsiness). It is not adequate to administer a low-dose adjuvant analgesic drug and consider it ineffective. If the first adjuvant analgesic drug is effective to some degree, other adjuvant analgesic drugs should be added. However, the combination of such drugs may increase problems regarding adverse reactions rather than effects; caution is needed.

As an oral medication, pregabalin, duloxetine, and amitriptyline are mainly used. With a parenteral route, ketamine and lidocaine are used. Steroids are used as adjuvant analgesic drugs when effects on edema, such as nerve compression, are expected.

e. Management of breakthrough pain

Concerning breakthrough pain, it is important to recognize that the exacerbation of pain (a few times a day) remains after the relief of persistent pain in many cases. Patients should be instructed to arrange an environment to promptly take a rescue dose at the onset of pain. In such cases, it is necessary to evaluate whether rescue doses are used to control anxiety, fear about pain, or physical symptoms other than pain.

Initially, a sufficient dose at which analgesic effects are obtained is necessary. The dose of an oral rescue dose to be used at the onset of pain is approximately 1/6 of a daily opioid dose. For continuous subcutaneous/intravenous administration, a rescue dose, that is effective for pain without adverse events, should be titlated.

An adequate administration interval is also important. Based on the time-to-maximum blood concentration (Tmax) and half-life of concentration in the plasma, administration interval of rescue opioids of oral and continuous subcutaneous/intravenous are 60 and 15 to 30 minutes, respectively.

If the interval until the peak of breakthrough pain is short (e.g., pain related to bone metastasis), switching to continuous infusion or the use of transmucosal immediate-release fentanyl should be considered. Concerning the single dose of this drug, a requirement should be individually titrated, but not be converted from a daily dose.

2. Treatment other than pharmacological management

a. Radiotherapy

Radiotherapy is a treatment for the cause of pain related to bone metastasis. If its effects are obtained, the dose of an analgesic drug may be reduced, or the administration of the drug may be discontinued. In particular, the presence of bone metastasis should be considered in patients with advanced cancer. If pain related to bone metastasis is suspected, diagnostic imaging should be performed as promptly as possible, and radiotherapy should be considered.

Palliative radiotherapy should be performed according to "Radiation Treatment Planning Guidelines in 2016 (section 10. Palliative care, in Japanese)" published by the Japanese Society for Radiation Oncology https://www.jastro.or.jp/medicalpersonnel/guideline/2016/10palliative_care.pdf.

b. Nerve block

If the site of pain is localized, analgesia may be achieved by nerve block involving the site alone. Concerning epidural or peripheral nerve block, if temporary analgesic effects are obtained by the single-dose administration of a local anesthetic, a continuous analgesic procedure may be considered: a catheter is inserted into a target site, and a local anesthetic with/without an opioid is continuously administered. Some types of nerve block exhibit long-term analgesic effects through nerve destruction with a neurolytic (such as phenol glycerin) or radiofrequency rhizotomy. Nerve block methods for the site and etiology of pain are summarized in Table 4.

If high-dose opioids induce myoclonus or consciousness disturbance, switching from oral/intravenous/subcutaneous administration to epidural or intrathecal administration should be considered. It has been reported that similar effects are obtained by epidural opioid administration at a 1/10 dose in comparison with intravenous/subcutaneous administration and by intrathecal administration at a 1/100 dose. In some patients requiring long-term catheter management, a reservoir is implanted.

Contraindications for nerve block include cancer infiltrating the site of nerve block/needle insertion route, the presence of an infectious focus, systemic infectious

diseases, and hemorrhage/coagulation disorder.

A nerve block can be performed safely (with a low risk of complications) when the general condition is relatively maintained. Therefore, if pain to be treated is present regardless of the dose of an opioid, the physician should consult a pain specialist early to examine whether the nerve block is adequate.

If an anesthesiologist/pain specialist experienced in cancer pain treatment can be accessible, many specialized block procedures can be available, but all block procedures cannot be performed in all medical institutions. However, efforts to search for methods that can be conducted in a treatment environment are important. For example, an epidural block is routinely performed in the field of anesthesiology and can be conducted in many institutions. Brachial plexus block, femoral nerve block, and peripheral nerve block, such as ischiatic nerve block, are often performed under the surgical procedure. If an anesthesiologist can be accessible, such a relatively common type of nerve block should be initially discussed. If the procedure is possible, it can be conducted as transient analgesia (bridging analgesia) until referral to a medical institution where specialized nerve block is provided.

Table 4　Nerve block

Site of pain	Etiology of pain	Block procedure
Upper limb	Brachial plexopathy related to Pancoast tumors or lymph node swelling Nerve infiltration of cancer and morbid fracture of cervical vertebra, humerus, or shoulder joint	Epidural block Intrathecal analgesia Root block Brachial plexus block
Lumbar/lower limb	Lumbosacral plexopathy related to minor pelvic visceral tumors or lymph node swelling, malignant psoas syndrome Nerve infiltration of cancer and morbid fracture of lumbar vertebra, sacral vertebra, pelvic bone, or thighbone	Epidural block Intrathecal analgesia Root block Femoral nerve block/ischiatic nerve block
Lower back	Myofascial pain	Trigger point injection
Thoracic region	Nerve infiltration related to thoracic vertebral or costal metastasis, and morbid fracture Pleural or thoracic wall infiltration (localized)	Epidural block Intrathecal analgesia Intrathecal phenol block Root block Intercostal nerve block
Upper abdomen	Capsular extension by liver cancer Pancreatic cancer pain Mesenteric infiltration, periaortic lymph node swelling Abdominal wall metastasis	Epidural block Celiac plexus block
Lower abdomen	Visceral pain related to colonic, rectal, vesical, uterine, or ovarian cancers Abdominal wall metastasis	Epidural block Inferior mesenteric artery plexus block
Pelvic region	Visceral pain related to rectal, prostatic, vesical, uterine, or vaginal fornix cancers	Upper/lower abdominal plexus block
Anal/perineal pain	Anal pain after rectal amputation, anal/perineal infiltration of recurrent rectal cancer	Impair ganglion block Intrathecal phenol block (saddle block with phenol glycerin)

Prepared based on " the Guidelines for Interventional Treatment for Cancer Pain edited by the Japan Society of Pain Clinicians

https://www.jspc.gr.jp/Contents/public/pdf/shi-guide04_08.pdf, in Japanese