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Review Article

Recent Developments in the Management of Cancer Pain in Japan: Education, Clinical Guidelines and Basic Research

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The Cancer Control Act of Japan came into effect in 2007. Most physicians, however, have not yet had sufficient opportunity to learn about pain management and other clinical palliative care practices. In an attempt to rectify this situation, the Japanese Society for Palliative Medicine has initiated the Palliative care Emphasis program on symptom management and Assessment for Continuous medical Education project. The two major roles of this project are to establish a faculty development program in palliative care, and to provide support for conducting workshops about basic palliative care throughout Japan. Another important movement is the development of a clinical guideline for the management of cancer pain. The Japanese Society for Palliative Medicine developed a clinical guideline for the pharmacological management of cancer pain in 2010. On the other hand, although clinical experience has demonstrated that psychological dependence is not a major concern when morphine is used to control pain in cancer patients, undue anxiety about psychological dependence on morphine in cancer patients has led physicians and patients to use inadequate doses of opioids. In an attempt to remedy this situation, therefore, Japanese basic researchers are cooperatively involved in conducting high-quality basic research to answer clinical questions in palliative care. They have demonstrated to the world, for the first time, that (i) chronic pain dramatically attenuates the reward effects of opioids and that (ii) atypical antipsychotics, such as olanzapine, can suppress morphine-induced emesis and alleviate the sleep dysregulation associated with neuropathic pain in animals. Thus, we are working in close collaboration to establish new strategies for palliative care in Japan.

Key words: palliative care – cancer pain management – education – basic research – Japan

INTRODUCTION

Cancer imposes a great burden on both the patients and their families or caregivers. Although a number of cancer symptoms may contribute to this burden, pain is one of the most distressing symptoms in cancer patients, regardless of the stage or type of the disease. Also, the prevalence of pain is crucial. Unrelieved pain in cancer patients may result in undesirable discontinuation of anticancer treatment and interfere with achieving a peaceful end of life. Thus, the management of cancer pain is an essential component of oncology care, and relief from cancer pain is largely contingent on the competency and compassion of the oncologist (1).

This review provides an overview of the prevalence of cancer pain, the physician's attitude to and knowledge about cancer pain, and recently developed activities for managing cancer pain in Japan.

PREVALENCE OF CANCER PAIN IN JAPAN

Recent systematic reviews have reported that the overall prevalence rate of cancer pain is 53–71% (2,3). The prevalence of cancer pain may be influenced by the type of cancer and the setting and extent of the disease. Previous studies from around the world have reported the prevalence of pain in different stages of the disease, as follows: 28–38% in newly diagnosed cancer patients (4–6), 36–59% in patients undergoing anticancer treatment (3,7) and 45–64% in patients with advanced, metastatic or terminal disease (2,3). Even among patients who have received curative treatment, a group recently known as 'cancer survivors', an estimated 33% suffer from pain (3).

However, there are few studies about the prevalence of pain in cancer patients in Japan. Yamagishi *et al*. (8) reported that ~60% of 1493 advanced cancer patients who were being followed up at outpatient oncology clinics in four different regions in Japan suffered from some degree of pain. In another study, around 15% of cancer patients who were receiving outpatient chemotherapy at one Japanese general hospital suffered from moderate to severe pain (9,10). However, to date, precise data on the prevalence of pain in inpatient settings (oncology wards and palliative care units), home care settings and cancer survivors in Japan are still lacking. Further studies are needed to clarify the prevalence of pain in Japanese cancer patients in different settings.

ATTITUDES AND KNOWLEDGE LEVELS AMONG PHYSICIANS IN JAPAN

The World Health Organization has identified cancer pain as a global health concern (11). A previous study suggested that 42% of cancer patients were under inadequate analgesia (12). Also, Okuyama *et al*. reported that Japanese oncologists' recognition of pain in their patients was suboptimal (13). A recent report suggested that among the significant obstacles to adequate pain control are professional barriers, such as lack of knowledge of the proper doses and adverse effects of analgesics, and misconceptions about addiction and tolerance (1).

With regard to the situation in Japan, the Japan Medical Association reported the physicians' attitude to palliative care in cancer medicine, based on the responses from 97 961 physicians working at hospitals or outpatient clinics all over Japan (14). This report showed that 47% of outpatient clinic and 72% of hospital physicians were willing to become involved in palliative care, including pain control. Furthermore, only 13% of outpatient clinic and 25% of hospital physicians felt that their knowledge and skill in respect of cancer pain control were sufficient. Actually, >50% of the respondent physicians harbored incorrect notions with regard to cancer pain control, such as 'opioid analgesics often cause addiction', 'opioid analgesics affect the prognosis' and/or 'pentazocine rather than full opioid agonists should be used to treat mild cancer pain'. Also, about a half of all the physicians felt that they were too busy to provide palliative care and <30% felt that it was easy to receive support from palliative care specialists. Thus, it is necessary to undertake education programs to spread basic knowledge about pain control and other palliative care issues in cancer patients, and to establish a system for the provision of support by palliative care specialists.

EFFECTS OF EDUCATION PROGRAMS ON PALLIATIVE CARE IN JAPAN

As mentioned above, one of the major barriers to adequate pain control is physicians' lack of knowledge and skill in pain control. Although a previous study showed that conducting workshops might improve physicians' knowledge about and attitude toward pain control (15), most physicians have still not had sufficient opportunity to learn about pain control and other palliative care issues during their medical training. To amend this situation, the Japanese Society for Palliative Medicine (JSPM) initiated the Palliative care Emphasis program on symptom management and Assessment for Continuous medical Education (PEACE) project in 2008, in cooperation with the policies of the 'Cancer Control Act' of the Japanese Government. The overall goals of the PEACE project are to enhance physicians' competency in palliative care and to foster a commitment to improving care for cancer patients. Toward this end, the two major roles of this project are to establish a faculty development program in palliative care and to provide support for conducting workshops about basic palliative care throughout Japan. The curricula of the workshops organized by the PEACE project include general remarks, management of pain and other major symptoms, communication skills and regional collaboration in patient care. Until December 2011, 2065 physicians had completed the faculty development course, 1592 workshops had been held and 29 736 physicians had attended the workshops. To explore the effects of these workshops, Yamamoto *et al*. distributed a questionnaire on these occasions to 217 physicians who attended a workshop, before they attended, and just after and 2 months after they had attended the workshop (16). The results showed that the physicians' knowledge had improved significantly after they had attended the workshop and that this improved knowledge was sustained for at least 2 months. Also, the physicians' difficulties in managing the symptoms decreased significantly by 2 months after they had attended the workshop.

DEVELOPMENT OF A JAPANESE CLINICAL GUIDELINE FOR CANCER PAIN

Another important measure to improve the quality of cancer pain management is the development of a clinical guideline. As a part of worldwide efforts to improve the quality of pain control, multiple clinical guidelines have been published for the management of cancer pain (17–22). In Japan, the JSPM first published a clinical guideline for the management of cancer pain in 2000. Thereafter, numerous clinical studies have been carried out on cancer pain management, multiple new drugs have been introduced in Japan and the methodology of development of guidelines has become more refined. Thus, the JSPM decided to develop a novel clinical guideline for the pharmacological management of cancer pain in Japan. First, the task group gathered clinical questions based on a questionnaire survey of all the members of the task group. These items were then restructured into 65 questions. Next, the task group performed a systematic literature review for each clinical question using the electronic search of PubMed, a hand search of all 'Journal of Pain and Symptom Management' and 'Palliative Medicine' articles published from January 2000 to July 2008, a search of the PaPaS (Pain, Palliative and Supportive Care) category of the Cochrane database, and a review of the reference literature of relevant guidelines (17–22) and textbooks (23–28). The review included only studies that evaluated the drugs available in Japan. After the systematic literature review, three sequential sessions of discussions using the Delphi method and an external review, a clinical guideline was established in 2010. The task group ultimately prepared 65 recommendations (24 recommendations for the management of cancer pain, 15 recommendations for specific management of opioid-induced adverse effects, 2 recommendations for patient education and 24 recommendations for the management of pain from specific etiologies). The general background descriptions and detailed descriptions of the recommendations are available at http://www.jspm.ne.jp/guidelines/pain/2010/index.php (in Japanese only). The majority of the recommendations are shown in Table 1. The clinical efficacy of this clinical guideline still needs to be assessed by a prospective study, e.g. an audit study investigating physicians' recording and exploring knowledge through educational seminars.

SCIENTIFIC CONTRIBUTION TO PALLIATIVE CARE BY BASIC RESEARCH IN JAPAN

In Japan, basic researchers are dedicated to conducting high-quality basic research to answer clinical questions in palliative care by effectively using the latest scientific skills. Although morphine and other μ-opioid agonists, such as fentanyl and oxycodone, are frequently used in the treatment of cancer pain and also of moderate-to-severe non-cancer pain, there is potential for abuse of and/or addiction to these drugs; this is considered to have complicated the use of μ-opioid agonists in the treatment of severe pain. However, clinical studies have shown that when μ-opioid agonists were appropriately used to control pain, actual abuse or addiction did not usually occur. The finding reported by Suzuki and Narita's (29–37) laboratories proved to the world, for the first time, that sustained pain resulted in a decrease in the abuse potential of morphine in severe pain states by a neuroadaptive mechanism. Basic researchers in Japan are conducting further investigations of the molecular mechanisms underlying the suppression of opioid abuse under severe pain states.

μ-opioid agonists have marked effects on mood and motivation. They can produce euphoria in humans and function as positive reinforcers (i.e. they can sustain drug-seeking behaviors). These reinforcing effects by μ-opioid agonists can become the primary stimuli that motivate behavior, with subsequent compulsive drug-seeking behavior or addiction. The mesolimbic dopaminergic system, projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), is a crucial network involved in the reinforcing effects of μ-opioid agonists (38). Positron emission tomographic studies in humans have mapped μ-opioid receptor distribution in the brain and have detected substantial receptor densities in areas involved in pain response (e.g. the insular cortex and thalamus) and also in reward-related areas (e.g. the cingulate cortex, mesolimbic system including NAc) (39). Under the conditioned place preference paradigm, intra-VTA administration of morphine produces a reward effect in animals (40,41). This place preference by morphine can be blocked by either dopamine antagonists or neurochemical destruction of the NAc (42). On the other hand, κ-agonists, including the endogenous neuropeptide dynorphin A (1–17), decrease dopamine release in the terminal fields of the nigrostriatal and mesolimbic systems, and can also block the reward effects of μ-opioid agonists (40,42) (Fig. 1). Repeated administration of μ-opioid agonists upregulates the expression of the κ-opioid receptor and prodynorphin mRNAs in the brain (43), and this upregulation might decrease the reward effects and potential for abuse of chronic μ-opioid agonists in clinical settings. Furthermore, pain stimuli themselves in the formalin model decreased the reward effects of morphine, and this effect was sensitive to κ-receptor antagonism and dynorphin antibodies in the NAc (37).

Like inflammatory pain, the release of dopamine in the NAc after morphine treatment is markedly suppressed by sciatic nerve ligation, a model of neuropathic pain (31). Under these conditions, neuropathic pain induced by sciatic nerve ligation leads to a reduction in μ-opioid receptor function to activate its G-protein in the VTA, resulting in the inhibition of the reward effect of morphine (31). One mechanism for the aforementioned reduction in μ-opioid receptor signaling in the VTA under neuropathic pain states could be a sustained increase in the release of the μ-opioid neuropeptide, β-endorphin. In fact, sciatic nerve ligation

Table 1. Recommendations listed in the guideline

1. Management of cancer pain

1.1 *Assessment*

1.1.1 Comprehensive assessment of pain should be carried out. A comprehensive assessment includes the assessment of the etiology of pain and the assessment of pain itself

1.2 *Patients with mild pain*

1.2.1 Acetaminophen should be used in cancer patients with mild pain [1A]

1.2.2 NSAIDs should be used in cancer patients with mild pain [1B]

1.2.3 The type of the non-opioid analgesics should be chosen according to the effectiveness and tolerability for individual patients [1A]

Prostaglandin E1 analog, proton pump inhibitor or H2 receptor antagonist should be used in patients who are treated with NSAID [1A]

1.3 *Patients with moderate-to-severe pain or inadequately controlled pain despite non-opioid analgesic*

1.3.1 Opioids should be used in cancer patients with moderate-to-severe pain or inadequately controlled pain despite non-opioid analgesics [1B]

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

1.3.3 In cancer patients with stable and not severe pain, either a sustained-release or immediate-release opioid may be used. In cancer patients with severe or unstable pain, an immediate-release opioid or parenteral opioid may be used [2B]

1.3.4 Patients should be carefully assessed and observed for nausea/vomiting when starting opioids, and anti-emetics should be prepared to be available whenever nausea/vomiting occurs [1C]

1.3.5 Patient should be carefully assessed and observed for bowel movement and provided instructions for adequate fluid intake and diet and administration of laxatives for the prevention of constipation when starting opioids [1C]

1.3.6 Non-opioid analgesics may be continued when opioids are introduced in patients with inadequately controlled pain with non-opioid analgesics [2B]

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

1.4.1 Non-opioid analgesics should be used concurrently with opioids in patients with inadequately controlled pain despite initial opioid use [1A]

1.4.2 The dose of regular opioids should be increased in patients with inadequately controlled pain *despite* initial opioid use [1B]

1.4.3 The type of opioid should be changed in patients with inadequate pain control under a certain type of opioid [1B]

1.4.4 Another type of opioid may be added in patients with inadequate pain control under a certain type of opioid, in consultation with an expert [2C]

1.4.5 An Administration route may be changed to intravenous or subcutaneous infusion in patients with inadequate pain control with oral or transdermal administration of opioid analgesics [2C]

1.4.6 Ketamine may be used in combination with opioids in patients with inadequately controlled pain after increasing opioids, in consultation with an expert [2B]

1.4.7 Corticosteroids may be used in combination with opioids with careful attention to the risk of adverse reactions in patients with inadequately controlled pain after increasing opioids, in particular pain etiologies [2C]

1.5 *Patients with breakthrough pain*

1.5.1 An rescue dose of an opioid should be used in patients with breakthrough pain [1B]

1.5.2 The rescue dose may be increased within acceptable adverse events, when the initial rescue dose provides inadequate analgesic effect [2C]

1.5.3 The dose of regular opioids should be increased or the interval of regular opioids should be shortened in patients with end-of-dose failure [1B]

2. Treatment of adverse events of opioids

2.1 *Nausea/vomiting*

2.1.1 The etiology of nausea/vomiting should be assessed, and any possible etiology should be treated

2.1.2 Anti-emetics should be used in patients developing nausea/vomiting on opioids. Type of anti-emetic should be chosen from anti-dopaminegics, porykinetics or antihistaminics [1C]

2.1.3 The type of opioid should be changed in patients developing nausea/vomiting on a certain opioid [1B]

2.1.4 The administration route may be changed to intravenous or subcutaneous infusion in patients developing nausea/vomiting on oral opioids [2C]

2.2 *Constipation*

2.2.1 The etiology of constipation should be assessed, and any possible etiology, especially fecal impaction or bowel obstruction, should be treated

2.2.2 Laxatives should be used in patients developing constipation on opioids [1B]

2.2.3 The type of opioid should be changed to fentanyl in patients on morphine or oxycodone with refractory constipation after laxatives [1B]

2.3 *Drowsiness*

2.3.1 The etiology of drowsiness should be assessed, and any possible etiology should be treated. The possibility of opioid overdose should also be assessed

2.3.2 Psycho-stimulants may be used in patients developing drowsiness on opioids, in consultation with an expert [2C]

Continued

Table 1. *Continued*

2.3.3 The type of opioid should be changed in patients with drowsiness on a certain opioid [1B]
2.3.4 An administration route may be changed to intravenous or subcutaneous infusion in patients developing drowsiness on oral opioids [2C]
2.4 *Delirium*
2.4.1 The etiology of delirium should be assessed, and any possible etiology should be treated
2.4.2 Anti-psychotics may be used in patients developing delirium on opioids [2B]
2.4.3 The type of opioid should be changed in patients with delirium on a certain opioid [1B]
2.4.4 An administration route may be changed to intravenous or subcutaneous infusion in patients developing delirium on oral opioids [2C]
3. Patient education in cancer pain management
3.1.1 Patients should be given education about cancer pain management [1A]
4. Treatment of pain from specific etiology
4.1 *Neuropathic cancer pain*
4.1.1 Any of the adjuvant analgesics (anti-convulsants, anti-depressants, antiarrhythmics, ketamine or corticosteroid) should be used in cancer patients with neuropathic pain [1B]
4.1.2 Another type of adjuvant analgesic may be added in patients with inadequate control of neuropathic pain after sufficiently increasing the dose of the certain adjuvant analgesicAQ, in consultation with an expert [2C]
4.2 *Bone metastatic pain*
4.2.1 Bisphosphonate may be used in patients with pain from bone metastasis, in consideration of the expected prognosis [2B]
4.3 *Epigastric pain due to pancreatic cancer*
4.3.1 A celiac plexus block may be performed in patients with epigastric pain due to pancreatic cancer [2A]
4.4 *Pain in the thoracic area*
4.4.1 A nerve block (such as epidural block, intercostal nerve block, nerve root block or intrathecal phenol block) may be performed in patients with pain in the thoracic area [2C]
4.5 *Perineal pain*
4.5.1 A saddle block or superior hypogastric plexus block may be performed in patients with perineal pain [2C]
4.6 *Pain from malignant psoas syndrome*
4.6.1 Muscle relaxants may be used in patients with malignant psoas syndrome [2C]
4.6.2 A nerve block (such as epidural block or nerve root block) may be performed in patients with malignant psoas syndrome [2C]
4.7 *Pain from malignant bowel obstruction*
4.7.1 Octreotide or scopolamine butylbromide may be used in patients with pain from malignant bowel obstruction [2B]
4.7.2 Corticosteroids may be used in patients with pain from malignant bowel obstruction [2B]

suppresses the place preference induced by systemic morphine along with a reduction in μ-opioid receptor function to activate its G-protein in the VTA, and these phenomena are abolished in β-endorphin-knockout mice (44). In addition, nerve ligation resulted in the inhibition of systemic morphine-induced dopamine release in the NAc, which is consistent with the reduced potential for abuse of μ-opioid agonists in this condition; this effect was also abolished in β-endorphin-knockout mice (44). Sustained exposure to β-endorphin could result in the μ-opioid receptor phosphorylation and uncoupling of receptors from effector systems, and thereby, desensitization. It is noteworthy that β-endorphin tends to cause greater desensitization than exogenous ligands such as morphine (Fig. 2). A serine/threonine kinase, G protein receptor kinase 2 (GRK2), has been shown to promote μ-opioid agonist-induced phosphorylation. The level of membrane-bound GRK2 in the VTA, but not in the pons or medulla, was increased in nerve-ligated mice relative to that in the controls (31). This increase in GRK2 in the VTA might therefore reduce μ-opioid receptor activity during sciatic nerve ligation, leading to an apparent decrease in morphine-induced reward effects. Taken together, these findings obtained from basic research could explain the mechanism underlying the suppression of opioid abuse under severe pain.

The use of opioids for cancer pain management is often associated with nausea and vomiting. Nausea and vomiting are controlled by the 'vomiting center' in the medulla oblongata (45), which receives signals from the chemoreceptor trigger zone (CTZ) in the area postrema, the gastrointestinal tract, the vestibular apparatus in the temporal lobe and the cerebral cortex (46). Opioids exert an emetogenic effect by stimulating the CTZ and the vestibular apparatus, and by inhibiting gut motility (47). Although the stimulation of the CTZ by opioids involves μ- and δ-opioid receptors (48), signals from the CTZ to the vomiting center mainly involve dopamine D_2 and serotonin (5-HT_3) receptors. Furthermore, opioid-induced stimulation of the vestibular apparatus and

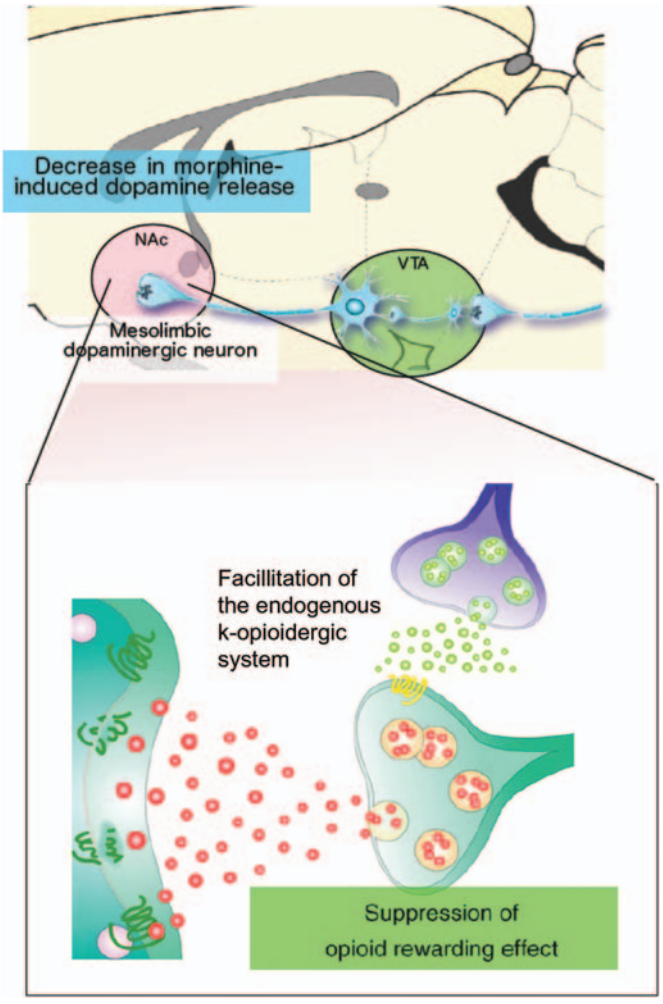

Figure 1. Schematic illustration of mechanism(s) in the inflammatory pain state. The opioid-induced reward effect is suppressed under an inflammatory pain state owing to the inhibition of dopamine release at dopaminergic terminals caused by the facilitation of the endogenous κ-opioid system within the nucleus accumbens (NAc) (modified from Niikura K. *Trends Pharmacol Sci* 2010;31:299–305).

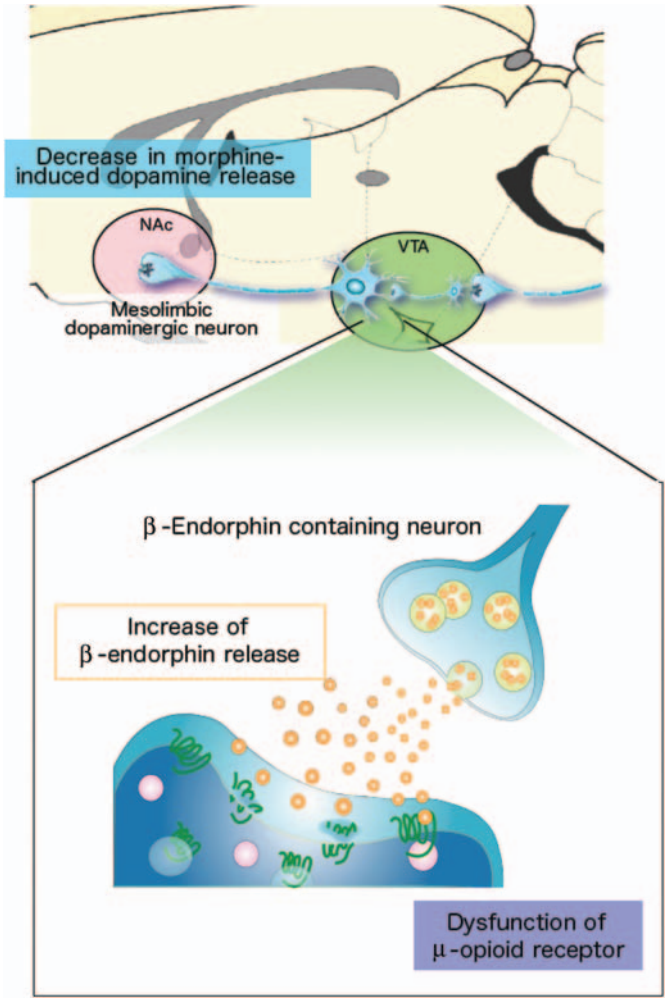

Figure 2. Schematic illustration of mechanism(s) in the neuropathic pain-like state. Peripheral nerve injury can cause sustained activation of the endogenous β-endorphinergic system in the brain. β-Endorphin released by chronic nociceptive stimuli can continuously activate μ-opioid receptors in the ventral tegmental area (VTA), thus leading to downregulation of μ-opioid receptor function and resulting in a decrease in dopamine release in the NAc (modified from Niikura K. *Trends Pharmacol Sci* 2010;31:299–305).

the subsequent sensory input to the vomiting center have both been suggested to involve histamine H_1 and muscarinic acetylcholine pathways (49). Atypical antipsychotics are more effective for the treatment of the positive symptoms of schizophrenia, such as hallucinations and delusions, than for alleviating the negative symptoms, such as lack of motivation and social withdrawal. Olanzapine is a newer atypical antipsychotic that blocks dopaminergic, serotonergic, adrenergic, histaminergic and muscarinic receptors mediating the actions of multiple neurotransmitters. Because it has an effect on the actions of neurotransmitters that are associated with nausea, it may have potential efficacy as an antiemetic medication. Based on these backgrounds, 'the basic research team in Japan' investigated the effects of olanzapine on morphine-induced emesis in animals. Olanzapine has been demonstrated to show high affinity for the muscarinic M1 receptor in animal brain tissues (50). Intriguingly, olanzapine decreased morphine-induced nausea and vomiting in a dose-dependent manner (50), although at the dose at which it exerted the antiemetic effect, it did not induce catalepsy or hyperglycemia (50). In addition, olanzapine, at this dose, had no effect on the morphine-induced release of dopamine or the inhibition of gastrointestinal transit (50), indicating that olanzapine may be useful for the treatment of morphine-induced emesis.

Insomnia is a common problem among people with severe pain (51). Sleep problems and daytime sleepiness seem to be related to depression and the severity of pain (52). Cortical GABAergic neurons form a part of the neurobiological substrate that underlies homeostatic sleep regulation. In animals, sciatic nerve ligation caused an increase in wakefulness and decrease in non-rapid eye movement sleep (53). Under these conditions, the expression of membrane-bound GABA

transporters (GATs) was significantly increased on activated glial fibrillary acidic protein-positive astrocytes in the cingulate cortex, and extracellular GABA levels in this area rapidly decreased after depolarization by nerve injury (53). Furthermore, sleep disturbance induced by sciatic nerve ligation was alleviated by the injection of a GAT-3 inhibitor into the intracingulate cortex (53). These findings provide novel evidence to show that sciatic nerve ligation decreases extracellularly released GABA in the cingulate cortex of mice. These phenomena may explain, at least in part, the insomnia in patients with neuropathic pain.

It has been established that benzodiazepines decrease wakefulness through enhancing the binding affinity of endogenous GABA to $GABA_A$ receptors (54,55). Considerable evidence indicates that benzodiazepines, such as midazolam, cannot independently elicit the influx of Cl^- ions through the $GABA_A$ receptor, but rather facilitate the actions of endogenous GABA by increasing the frequency of channel opening, whereas barbiturates, on the other hand, can directly open $GABA_A$ receptor-associated chloride channels in the absence of GABA (56,57). In an experimental model of neuropathic pain, nerve injury suppressed the hypnotic effect of the benzodiazepines, but not that of pentobarbital, in association with decreased GABAergic transmission in the cingulate cortex (53). Interestingly, olanzapine inhibited thermal hyperalgesia and completely alleviated the sleep disturbance induced by sciatic nerve ligation (50). Against the background of increasing concern about 'polypharmacy,' olanzapine can be used as a single adjunctive agent and can be given at doses tailored to the clinical state of the patients, which would be expected to improve the quality of life of the patients while greatly reducing the side effects of opioids.

Overall, basic research in the field of palliative care in Japan is currently aimed at fostering a better global understanding of opioid analgesics and at creating new strategies for cancer pain treatment. Finally, it should be mentioned that such 'real' translational research performed in Japan is intended to answer clinical questions in palliative care.

CONCLUSION

Clinicians and basic researchers are able to cooperate on palliative care in Japan. The PEACE project, the novel clinical guideline, and the basic research are expected to improve the quality of life of all cancer patients. On the other hand, opioid analgesics are frequently used for the treatment of cancer pain and also for that of moderate-to-severe non-cancer pain. We hope that a drug selection algorithm classified by symptoms can be established soon. Based on scientific evidence, we need to reconsider, anew, the appropriate use of opioid analgesics for the treatment of cancer pain.

Conflict of interest statement

None declared.

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