Table 2 Responder's characteristics

	No. (%)
Responders	224
Sex	
Male	197 (87.9)
Female	27 (12.1)
Experience (years)	
Median	20
Range	6–52
Specialty	
Surgery	189 (84.4)
Medical oncology	30 (13.4)
Obstetrics and gynecology	1 (0.4)
No answer	4 (1.8)
Surgeries performed at the attending institution (2006)	
Median	80
Range	0–960

Table 3 Opinions on prolongation of postoperative pain (responses based on multiple choices)

Opinion	No.	%
Nothing can be done	33	14.8
Pain rarely occurred	19	8.5
There is no need for treatment	65	29.1
Pain will resolve with time course	109	48.9
I should focus on the cancer treatment because pain is a secondary symptom	14	6.3
It is difficult to explain to the patients	23	10.3
I want to do something for my patients	92	41.3
Pain needs to be treated	63	28.3
I want to know how it can be treated	112	50.2
I should consult a pain specialist	30	13.5
Other	12	5.4

Table 4 Recognition and duration of PMPS

	No.	%
Recognition of PMPS		
Known	158	70.5
Unknown	66	29.5
Duration of PMPS (years)		
1	11	5.0
3	52	23.4
5	27	12.2
7	5	2.3
More than 10	61	27.5
Unknown	66	29.7

Table 5 Current measures taken for PMPS patients (responses based on multiple choices)

Measures to be taken	No.	%
No treatment, with observation	145	65.3
Treat by myself	106	47.7
Alternative medicine	3	1.4
Let patients treat themselves in their own way	27	12.2
Consult pain specialist	69	31.1
Other	13	5.9

Table 6 Therapies currently used for PMPS patients (responses based on multiple choices)

Treatment	No.	%
NSAIDs	91	78.4
Opioids	10	8.6
Tranquilizers	38	32.8
Antidepressants	40	34.5
Herbal medicines	14	12.1
Topical preparations	31	26.7
Nerve blocks	10	8.6
Local injections	7	6.0
Rehabilitation	29	25.0
Acupuncture	0	0
Other	9	7.8

Table 7 Current treatment effects

	No.	%
Not effective	25	21.6
Slightly effective	56	48.3
Moderately effective	25	21.6
Very effective	2	1.7
Unknown	8	6.9

who responded "treatment is administered by myself" in the recognition group and unrecognizing group was 83 and 22, respectively, a significantly greater response by members of the recognition group than by the unrecognizing group ($p < 0.01$).

Patients were classified into an effective group (very effective or moderately effective) and an ineffective group (not effective or slightly effective) according to the therapeutic effect to compare the current treatment modality and its effects. For the NSAIDs, antidepressants, tranquilizers, and opioids that were frequently used in the treatment, the therapeutic efficacy is shown in Table 8. For all drug classes indicated for the treatment of PMPS, more

Table 8 Comparison of treatment effects by preparation

Treatment drug	Ineffective group[a, c]	Effective group[b, c]	I do not know[c]	Significance
NSAIDs	69	17	5	<0.01
$N = 91$	(75.8 %)	(18.7 %)	(5.5 %)	
Tranquilizers	33	2	3	
$N = 38$				
Antidepressants	31	6	3	
$N = 40$				
Opioids	7	3	0	
$N = 10$				

[a] Ineffective group (not effective or slightly effective)

[b] Effective group (very effective or moderately effective)

[c] Multiple choices

responders considered them to be ineffective than effective. Furthermore, the treatment with NSAIDs was significantly insufficient ($p < 0.01$).

Discussion

Postoperative chronic pain after mastectomy, PMPS, has been underestimated because physicians have considered that breast cancer surgery is superficial and minimally invasive, and therefore postoperative pain will resolve with time course. According to the present survey conducted in Japan, the incidence of chronic pain after breast cancer surgery was as high as 21–65 % (2–9 years after the surgery), and the pain remained for a long time. In spite of this, many patients are reported to have never been treated for the pain, and had given-up the idea of treating the pain, believing that their pain could not be alleviated. The report revealed that there are many patients suffering from pain who are left untreated [4, 5, 8, 17]. The current status may have been caused partly because the majority of breast cancer patients are women, because surgeons have little interest in pain, or because the treatment information is insufficient [5, 17, 21, 26]. As the WHO has proposed early stage palliative care for these patients, the status should be improved as soon as possible also in Japan because such chronic pain may have a big impact on the postoperative QOL of the patients. Furthermore, there are tendencies for both increase in incidence rate and improvement in the survival rate with regard to breast cancer in Japan.

In Japan, many of the physicians involved in breast cancer treatment belong to the Japanese Breast Cancer Society, and the society has established a system to certify specialists. Physicians who take care of postoperative breast cancer patients are among these specialists. Therefore, we made a request to the Japanese Breast Cancer Society specialists to survey recognition of PMPS and the present status of treatments.

Survey results on the recognition of physicians regarding PMPS have not yet been reported globally. Also, probably due to the limited number of studies, there have been no Cochrane Reviews regarding PMPS.

The response rate of the questionnaire was 34.7 %. This result could not be compared with other results, because no similar survey on recognition by physicians about chronic pain after cancer surgery had been conducted. In Japan, many of the physicians engaged in breast cancer treatment are surgeons, who perform not only surgery but also postoperative chemotherapy and hormone therapy in most cases. There were strong opinions concerning prolonged pain associated with surgery, such as: "I want to do something for my patients" (41.3 %); "I want to know how pain can be treated" (50.2 %); "pain needs to be treated" (28.3 %). On the other hand, there were also many moderate opinions, such as: "Pain will resolve with time course" (48.9 %); "there is no need for treatment" (29.1 %); "nothing can be done" (14.8 %). These opinions may be among the reasons treatments for postoperative chronic pain have not been actively performed in Japan despite the fact that many physicians were aware of the existence of prolonged postoperative pain.

The disease state of PMPS was known to as many as 70.5 % of the physicians. However, considering that most patients afflicted with breast cancer undergo surgery, this number may be low for physicians attending to the treatment of breast cancer. The most frequent incidence rate of PMPS considered by the physicians was 20 %, and the second was 40 %, showing lower incidence rates in Europe and the US (30–70 %) [8–11]. Although limited, some physicians responded that the incidence rate of PMPS was either 0 % or 80–100 %, revealing that some physicians believe that chronic pain does not occur, while others believe the great majority of the patients suffer from pain after surgery.

It seems to be well known that the duration of PMPS is long. Most physicians were attending 1–5 PMPS patients, the second most attending 6–10 patients, and the third most attending 11–20 patients. Estimating that 20–40 % of the patients who had undergone surgery were attended by physicians, we have an impression that the reported numbers were relatively small. Approximately 20–30 % of the physicians responded that they did not know the incidence or duration of PMPS, nor the number of PMPS patients, suggesting that physicians have paid little attention to PMPS. Approximately half of the physicians responded that they had difficulty with treating PMPS. The most frequently taken measure was follow-up observation alone (65.3 %). Although many physicians are aware of prolongation of chronic pain after breast cancer surgery, the rate

of follow-up observation alone was high. This may reflect the fact that a high percentage of physicians consider the pain will resolve with time course or that there is no need to treat the pain. This study revealed that the rate of treatment for PMPS was low in Japan and that this was caused by low recognition of PMPS by physicians. Accordingly, the outreach to physicians who may be likely to begin therapy for such patients is very important, as this will be of benefit for the patients. According to the International Association of Study for the Pain (IASP), PMPS is a neuropathic pain caused mainly by a disorder of the intercostobrachial nerve [6, 7]. The first-line drugs recommended for treatment are tricyclic antidepressants, pregabalin, or gabapentin, followed by local anesthetics, selective serotonin-noradrenaline reuptake inhibitors, and opioids [27–30]. In Japan, it is reported that antidepressants show high efficacy in retrospective study [17] but not in randomized study. Moreover, in the "2011 Clinical Practice Guideline of Breast Cancer" of The Japanese Breast Cancer Society, the item for PMPS has been set, and it recommends careful treatment against PMPS according to the guideline for the treatment of neuropathic pain, though the number of the randomized trials of the PMPS treatment is small across the world [31]. This suggests that, although it is well known among pain specialists that NSAIDs are not effective for neuropathic pain such as PMPS, some general physicians have not recognized it. According to the survey, antidepressants and therapeutic drugs for PMPS were used by 34.5 % of the physicians who treated the patients by themselves. As a whole, however, the survey revealed the current situation that NSAIDs, the least effective type of drug for PMPS, tranquilizers, nerve blocks, and local injections were often used. Furthermore, only 1.7 % of the physicians responded that the treatment was "very effective." Even when "moderately effective" was included, the response that the treatment was effective was only 22.9 %, revealing that the current treatment modality is not appropriate and an adequate response is not achieved. Furthermore, the result of treatment effects by drug category showed that significantly more physicians ($p < 0.01$) felt that NSAIDs are not effective or slightly effective, revealing that NSAIDs were administered to patients although the inefficacy of the treatment effect was recognized. This suggests that information on the treatment modality of PMPS is not widespread, and as pointed out in previous reports regarding other postoperative chronic pain, there are only a few reports regarding PMPS in surgery and treatment of breast cancer, and there is little information regarding the treatment in Japan, which also may cause this situation [32].

In addition, comparison of results of treatment effects by drug category showed that a high percentage of physicians also felt that the treatment effect was not sufficient even with antidepressants and opioids, which are therapeutic drugs for PMPS. This result suggests that it is likely that appropriate treatment with optimal dosage and administration is not performed even with these PMPS drugs. The fact is pointed out that many clinicians in Japan are also not familiar with the treatment of PMPS, which is the same as in Western countries [5, 8, 22].

While this survey had an advantage in that valuable comments were received from 224 experienced specialists, it has some drawbacks. First, the responses may be biased because most of the respondents are surgeons. Second, no information on non-respondents was available, as described above, and they could not be compared with respondents. Third, the possibility cannot be ruled out that more surgeons who are interested in pain answered questions than those who are not interested in pain. This may have resulted in a higher PMPS recognition rate or the number of answers indicating proactive attitude towards pain treatment. Finally, the response rate was 34.7 %, which accounts for only one-third of all recipients of the questionnaire. Survey methods by which views can be obtained from more surgeons and physicians need to be devised, and further surveys are necessary.

The present survey results indicated that currently in Japan, many PMPS patients might exist who are not provided sufficient treatment. If the satisfaction with treatment effect by physicians is as low as the current state, it is estimated that the patients' satisfaction would be even lower. The majority of physicians believe that information disclosure to patients is essential, which is a subject for future study. At the same time, this study revealed that physicians have received little information about the treatment of PMPS. Therefore, appropriate first steps are to provide correct information regarding appropriate diagnosis and treatment of PMPS, and to promote more studies on the treatment of PMPS in Japan. The results of this survey will be of use to improve the recognition and treatment of PMPS [18].

Conclusions

With the cooperation of the Japanese Breast Cancer Society, a survey on the current status of recognition and treatment of PMPS was conducted among the specialists of the society. According to the survey results, many physicians engaged in breast cancer practice recognized the incidence and duration of PMPS. However, sufficient treatment has not been provided to the patients, and currently treatment is performed using mainly NSAIDs, and the treatment effects are insufficient. It was revealed that currently appropriate treatment modalities have not been widely used. What is currently needed is to provide

appropriate information regarding PMPS to physicians, and then to provide the information to the patients and perform further studies on the treatments.

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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 ($5\text{-}HT_3$) receptors. Furthermore, opioid-induced stimulation of the vestibular apparatus and

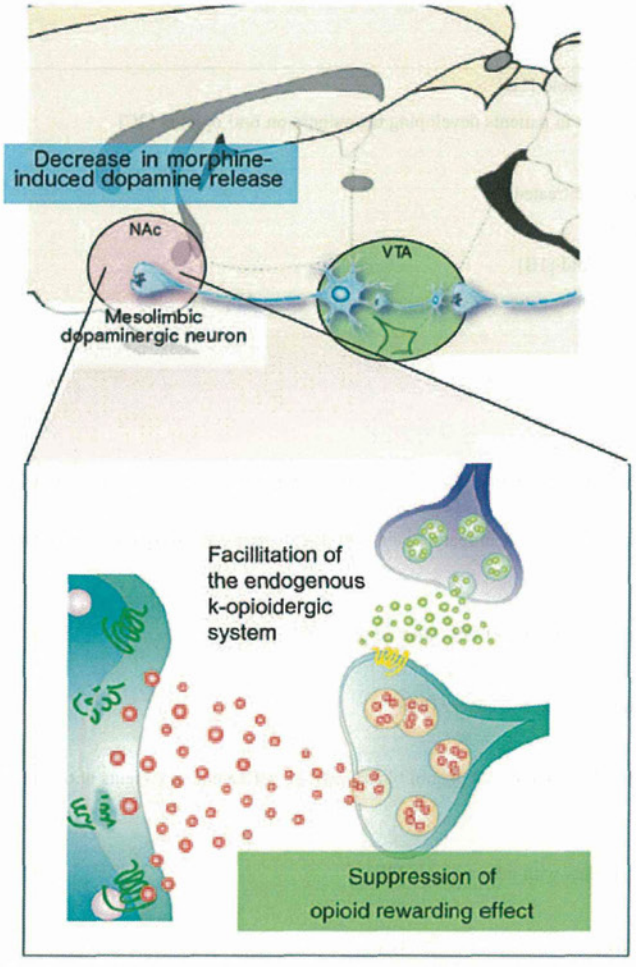

Figure 1. Schematic illustration of mechanism(s) in the inflammatory pain state. The opioid-induced reward effect is suppressed under an inflammatory pain state owing to the inhibition of dopamine release at dopaminergic terminals caused by the facilitation of the endogenous κ-opioid system within the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

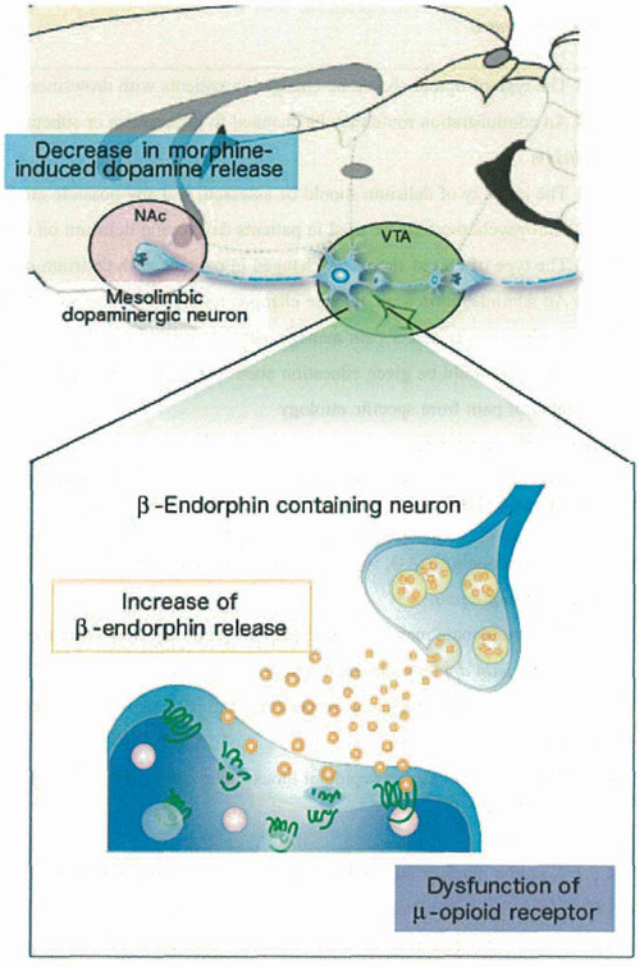

Figure 2. Schematic illustration of mechanism(s) in the neuropathic pain-like state. Peripheral nerve injury can cause sustained activation of the endogenous β-endorphinergic system in the brain. β-Endorphin released by chronic nociceptive stimuli can continuously activate μ-opioid receptors in the ventral 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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特集　オキシコドン製剤を使いこなす

がん疼痛治療の新しい選択肢，純粋オキシコドン注射剤―どういう症例に，どうやって使う？―

A new treatment option for cancer pain : pure oxycodone injection
― in whom and how should it be used ? ―

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Key Words

- がん疼痛(cancer pain)
- オピオイド(opioid)
- オキシコドン注射剤(oxycodone injection)
- パビナール®(pavinal®)
- タイトレーション(titration)
- 副作用(adverse effect)

Summary

新規発売の純粋オキシコドン注射剤(OXJ)について，治療戦略上重要な薬剤であること，OXJの導入適応，除痛に至る増量の方法，注意すべき副作用，の４点について自験例の解析報告を中心にして解説した。特に，適応は３つの導入パターン：①ルートスイッチ・パターン(経口オキシコドンからの投与経路変更を目的としたOXJ導入)，②ローテート・パターン(モルヒネによる副作用軽減あるいはフェンタニルの効果不十分例に対するOXJ導入)，③ナイーブ導入パターン(オピオイド未使用例(opioid naïve)にOXJ導入での鎮痛を図る)について詳細に述べた。本薬剤が日本の除痛率向上に寄与することが期待される。

In association with the new release of pure oxycodone injection (hereafter, OXJ), the following four issues are described based on our audit reports the importance of OXJ in treatment strategies, indications for OXJ injection, ways to increase doses for pain relief, and adverse reactions to which attention should be paid. Regarding indications in particular, the following three patterns of introduction are delineated and described specifically : ①Pattern of route switching (introduction of OXJ to change route of administration from oral oxycodone agent) ; ②pattern of rotation (introduction of OXJ to relieve adverse reactions associated with morphine, or introduction in cases with insufficient efficacy with fentanyl) ; ③pattern of naive introduction (in opioid-naïve patients who have no experience with opioids, intend analgesia with introduction of OXJ). It is expected that OXJ will contribute to improve the performance of cancer pain relief in Japan.

はじめに：がん治療医へのメッセージ

がん疼痛は，「オピオイド(いわゆる麻薬)」が必要となる激しいものが多い。これは，無秩序な正常組織への浸潤，破壊という他疾患にないがんの病因によるものと考えられる。オピオイドを「適切に」使わないと，耐えがたい痛みが死への恐怖とともに患者を苦しめることになる。わが国でがん死亡が年間30万人を超え，死因の第１位となって久しい。悲しい現実だが，進行・難治がんに対する治癒や寛解は困難な現状である。

それゆえに，がん治療に携わる全医師はがん疼痛治療も抗がん治療に劣らない「(現実的な)治療目標」なのだと認識してほしい。抗がん剤と同じように，国内で使用できる「オピオイド」の適応や使用法を学ぶのはプロの医療者としての責務と考える。そして，オキシコドン注射剤(OXJ)は，

よりよい除痛を達成するための強力な選択肢である。読者諸氏にはぜひともその使用法をマスターしてほしい。

本稿の情報リソースと目的について

筆者は，2003年から複方オキシコドン注射液(パビナール®注(PAV注))をがん疼痛治療に積極的に使用してきた。PAV注は90年以上前(大正時代)に発売された国産オピオイド注射剤で，複方(調合)の内容は1アンプル1mLにオキシコドン8mgとヒドロコタルニン2mgである。ヒドロコタルニンはコデイン類似のアヘンアルカロイド(オキシコドンのようにモルヒネ抽出過程の副産物)だが，麻薬指定は受けていない。単剤(内服鎮咳薬)として100mg/日程度が処方されていた記録があるが，PAV注の持続皮下投与(時間1mL程度が限界)では薬理作用は無視できると思われる。

がん疼痛治療にPAV注を使った報告は稀であり，筆者は自施設および共同研究グループ(SCORE-G(http://www.itaminai.net/scoreg/))にて行ったAudit研究(自験例の解析研究)を原著論文として公開し[1)2)]，またOXJの臨床試験と発表に協力させていただいた[3)]。

これらの情報を読者諸氏に役立つように集約し，新規薬剤の使い方のコツ・ヒントを提示したい。

具体的には，①どういう患者へ(選択基準)どうやって(具体的処方)，②起こりうる副作用を前もって，の2点について述べる。

どういう患者に対して導入を考える？：選択基準の3パターンと処方戦略を知ろう

1．背景知識：OXJ発売前に国内で使用可能であった3つの強オピオイド注射剤

OXJ発売前に日本で使用可能であった3種類の強オピオイド注射剤(モルヒネ注射剤，PAV注，フェンタニル注射剤)をどう使い分けるのがベストかについては，未確定である。つまり，処方医が個々の症例へ経験的に(使い慣れたものを選択して)使い分けている。よって現時点では，モルヒネ注射剤の消費量はほかの2剤よりも圧倒的に多いと思われる。OXJがなぜ必要かを理解するために，先行発売注射剤の背景知識を以下に示す。

・モルヒネ注射剤は，治療医，特に外科系医師にとって最も使い慣れた薬剤である。がん疼痛治療上，モルヒネの利点は多い。①鎮痛効果が高い(他製剤で鎮痛が得られないときに切り替えると改善することがある)，②重症例でオピオイド大量投与が必要になっても高用量製剤(4％5mL，200mg/アンプル)がある，③貼付以外の投与経路すべてに対応可能(内服，坐剤，静脈内投与，皮下投与，硬膜外，くも膜下)である，④注射は相対的に低コストである，などがある。欠点としては，肝臓を経由した代謝産物が薬理活性をもつために，①せん妄・幻覚・眠気といった中枢神経性副作用がやや多い，②社会通念的に乱用薬物との混同が根強い，③皮膚の痒み，筋不随意運動などが稀にみられる，などであろう。

・PAV注は非常に古くからある(1920年代発売)が，がん疼痛に使われることは稀であった。おそらく，①非がん疼痛や麻酔領域に限定して用いられてきた，②がん治療医に「馴染みのない」皮下投与しか適応がない，③添付文書の情

報が乏しく，インタビュー・フォーム(日本病院薬剤師会がメーカーに要請する補填的文書)もない，などが理由であると考える。また，混合されているヒドロコタルニンの薬理作用は無視できる[1]可能性が高いが，コデイン類似物質であるため肝転移や肝血流低下による血中濃度上昇の可能性も指摘されている[4]。皮下投与のみの保険適応ではあるが，添加物によるリスク回避の観点からも高用量の静脈内投与は推奨できない。

・フェンタニル注射剤も麻酔科領域で汎用されてきたが，①コストが高い(濃度が薄い)，②2004年までがん疼痛に対する保険適応がなかった，などの理由でがん治療医が選択する可能性は低いだろう。ただし，フェンタニル注射剤持続投与からフェンタニル貼付剤への直接切り替えが保険上認められたため，内服不能(例：イレウスや頭頸部がん)症例では消費が増える可能性はある。

2．OXJ導入を検討すべき3パターン：筆者の経験からの推奨

以下は，エビデンスに基づく知見や「これが正しい方法である」というわけでなく，筆者による投与経験の集約であることに留意されたい。

①ルートスイッチ・パターン(図1)…経口オキシコドン(オキシコドン徐放錠，オキシコドン速放散)からの投与経路変更(route switch)としての導入：「内服不能への対応手段」の1つとして，同じオキシコドンであるOXJへ切り替える方法。また，内服が可能となれば「内服へ戻す」経路変更も検討する。

②ローテート・パターン(図2)…副作用の軽減，または鎮痛の改善を期待して使用中のオピオイドをOXJに切り替える，いわゆるオピオイドローテーション：モルヒネ注射剤によるせん妄・傾眠で継続困難・増量不能で困ったとき，またフェンタニルでの鎮痛効果が不十分なときに検討されることが多い。

③ナイーブ導入パターン…初回オピオイド導入(opioid naïve)例に対するオキシコドンの薬理特性を活用した投与：モルヒネ注射剤に対する患者・家族の心理的抵抗が大きいとき，モルヒネ注射剤では腎障害・せん妄発生既往がありハイリスクと判断される場合に考慮する。また，将来オキシコドン徐放錠へ切り替える症例では利便性が高いだろう。

①ルートスイッチ・パターンについての解説

図1に，OXJを治療選択肢として「活用できた」典型的な症例を提示した。この症例は，嘔吐で電解質バランスが崩れ脱水状態となり，腫瘍増大のため疼痛が悪化して不安定な病態を呈していた。このような症例に対しては，モルヒネ注射剤へ切り替えて管理するのが国内では圧倒的大多数である。しかしこの方法は，上記のパターン①と②を同時に，しかも代謝や疼痛が不安定なときに行うことを意味する。よって，頻度は不明だが予期せぬ副作用の出現や疼痛管理が不十分になるといったリスクが予想される。パターン①(図1)のごとくOXJを用いて「同じ成分同士」で経路のみを切り替える方法は，より安全だと思われる。

国内の経口オピオイドは，モルヒネよりオキシコドンが主流となっている(国際麻薬統制委員会の統計データなどより)ので，OXJはこの役割が最も期待できる。われわれの報告でも，このパターンがOXJ導入の主たる理由として最多であった(文献1)で62.9%，文献2)で40.0%)。

経口剤の生体内利用率(bioavailability)，つまり100%吸収される静脈内投与に対して腸管から吸収される場合何%程度かという情報は，投与経路変更に必須である。在宅やホスピスを中心に麻薬投与ルートとして多用される持続皮下投与(皮下の毛細血管吸収)でも，強い炎症や浮腫がない限り静脈内投与と同じ100%と考えてよいだろう。経口オキシコドンの生体内利用率の報告は，オキシ

コドン注射剤との切り替え観察により得られている。具体的には①PAV注を用いた国内報告：われわれの単施設0.70[1]，多施設0.82[2]，丸山ら0.78[5]，国分ら0.71[6]，②今回発売されたOXJと同じ製剤を用いた欧米報告（OxyNorm injection®）：0.6（Kalso，1990），0.82（Rayhia，1991）などと報告されている。われわれの報告は皮下投与可能なドーズまで（時間投与1 cc程度以下）の生体内利用率の報告であり，OXJの大量投与や治験では確認できないハイリスク例（例：プレショック，感染症併発）では0.6の変換比率としてレスキュードーズ使用と集中的観察によるタイトレーションを行うべきと考える。

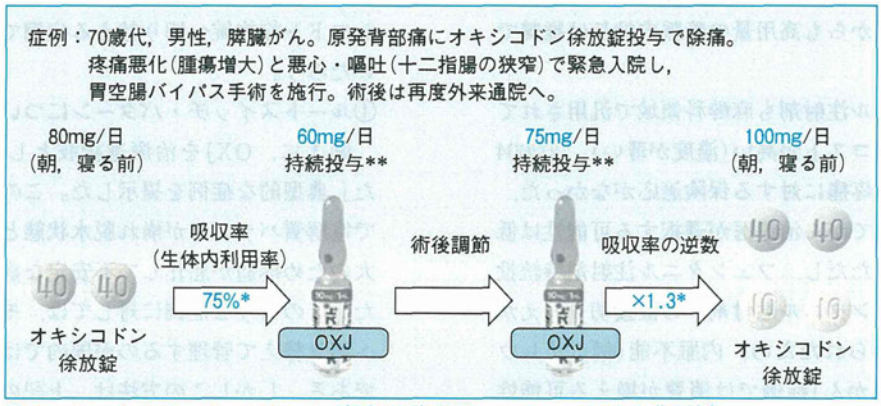

図1．ルートスイッチ・パターン（投与経路変更，route switch）の典型例
＊：吸収率（生体内利用率）は，各科報告で60～80%（逆数で1.3～1.7）と幅がある。
大量投与やハイリスク例（高齢，状態不良）では低めの換算比率が安全。
＊＊：内服でのレスキュードーズは1日量の6分の1程度，1時間間隔。注射では20～30分間隔で2時間分をフラッシュ投与。

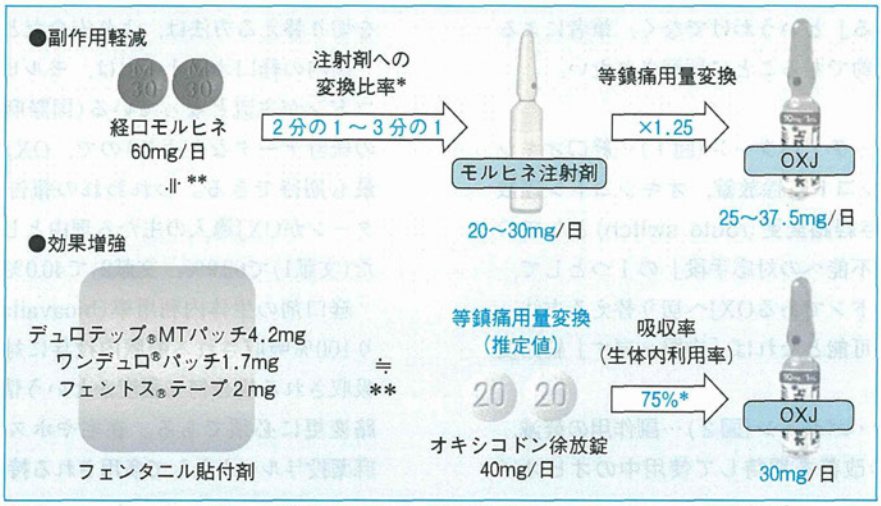

図2．ローテート・パターン（麻薬の変更，オピオイドローテーション）のサンプル
＊：生体内利用率は個体差が大きく，幅をもって安全な変換を要する。
＊＊：あくまで目安であり，高用量例では少量ずつ変換し，慎重な観察が必要である。

②ローテート・パターンについての解説

図2に，“オピオイドローテーション”を行う際の基本単位を示した。ルートスイッチ・パターンと同様に，生体内利用率や変換比率に関しては個体反応の差や代謝能力による差異が想像以上に大きい。本稿では理解のためシンプルに記載したが，変換比率は研究報告・成書とも幅をもって記載されている。読者諸氏はリスク管理に十分に留意していただきたい。

モルヒネ注射剤からOXJへの切り替えは，モルヒネの代謝産物蓄積による副作用(せん妄，傾眠)の軽減が主な目的である。欧米では，このメリットを利点として積極的にがん疼痛に利用している(米国Gagnon, 1990；オーストラリアAsyby, 1999)。国内でも，モルヒネ注射剤を部分的にPAV注へローテーションした際の有効性が報告されている[7]。また，経口モルヒネから経口オキシコドンへのローテーションによりモルヒネの副作用が軽減することが国内オープン試験で報告(奈良林，2009)されている。OXJへのローテーション効果を，日本人で確認する研究が期待される。

③ナイーブ導入パターンの解説

化学療法のくり返しや疾患進行で腎機能が低下した経口投与不能患者がオピオイド投与を要する強い疼痛を訴えるシチュエーションは，急性期病院において少なくないだろう。さらに，高齢で軽度のせん妄や傾眠がすでにある，術後せん妄の既往があるなどの場合，モルヒネ注射剤でなくOXJでの疼痛治療の適応があると思われる。OXJを使用し，病状と除痛効果が安定したことを確認してから経口オキシコドンへ移行する方法も同様に考慮する。すなわち，この患者の全身状態と疼痛が「将来どうなるか」を予測し，それに対し「最終的な疼痛管理をどうするか」という予定を立てる。

また，経口オキシコドンによる導入と同じことだが，「モルヒネではない(近い薬剤ではあるが)」との説明で患者・家族に心理的メリットがあるかもしれない。日本では，モルヒネと違法薬物のアヘン，大麻，覚醒剤を混同し恐怖している患者・家族はいまだに多い。

もう1つ，日常診療で筆者は神経障害性疼痛の因子が強い症例に対してはOXJでの導入を検討している(97例中2.1%)[1]。エビデンスとして，オキシコドンの糖尿病性神経障害性疼痛への有効性証明無作為化試験(Watson, 2003)，がん疼痛での有用性調査報告(Garcia, 2011)があるためである。

OXJを使って除痛達成のゴールに至るには

新規薬剤とはいえ，除痛のためのタイトレーション(用量調節)は従来のオピオイド注射剤と同じ方法でよい。高用量で30%～低用量で50%ほどのベース(1日量)増量するか，レスキュードーズ(頓用使用)の1日合計(または半分ほど)を上乗せする，などが経験的に実施されている。

むしろ問題になるのは目標の設定，「何をもってタイトレーション終了とするか」である。タイトレーションを始める前に，患者・家族・医療従事者にプランを事前説明している医師は多くない。しかし，WHO方式がん疼痛治療法のいう“きめ細かな配慮と説明”は必須である。到達点を理解してもらい共有することで，成功率が上がると考える。図3に，OXJのオープン試験の概略図を示した。臨床試験プロトコルなので日常臨床では厳格すぎるかもしれないが，非専門家の読者には参考になるだろう(図3)[3]。

また，持続注射(静脈，皮下)のレスキュードーズの用量は，1時間量を早送り(フラッシュ，ボーラス投与)するとした成書が多い。しかしわれわれは，図1のように経験則として2時間分(およそ1日量の10%程度)を目安としている。理由は，複数回レスキュードーズを使用しても効果

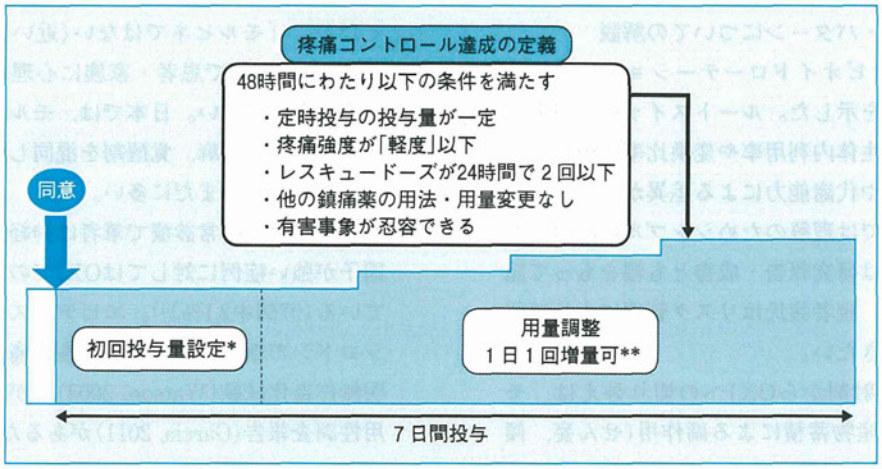

図3．OXJのオープン試験における疼痛コントロール達成の定義
＊：オピオイドナイーブ患者の初回投与量は10mg(7.5～12.5mg)，他オピオイドからOXJへの切り替えは治験で定められた換算比率に従って設定。
＊＊：4段階疼痛強度2点以上(0：無痛，1：軽度，2：中等度，3：高度)，あるいは24時間以内のレスキュードーズ(1日量の24分の1量を目安)が3回以上必要となった場合。

が実感できない場合，レスキュードーズの使用自体への不信感から逆プラセボ効果が起きる可能性があると考えているからである。2時間分を使用することにより考えられるリスクは，本人への説明や経過観察で回避できるだろう。

OXJを処方した医師および観察する看護師が留意するべき副作用と対策

今後キードラッグになるであろうOXJの「予想される副作用」と「その対策」を読者と共有することは有用であろう。詳細はOXJのインタビュー・フォームを参照されたいが，本稿では現場での「コツ」を簡潔に述べたい。リソースは，臨床試験の対象でなく急性期病院でのAudit報告[1]である。いわば，現場から現場へのメッセージとお考えいただきたい。

1．せん妄

OXJは，現在国内で汎用されているモルヒネ注射剤よりせん妄が少ないと考えられ，患者・家族はもちろん看護師にとってのストレス軽減が大いに期待される。モルヒネ注射剤を使用している患者のせん妄がPAV注への(部分的な)ローテーション・パターンにより改善した報告[7]もある。ただし，筆者のAuditで，PAV注からフェンタニル注射剤への切り替えを要した患者が少数(3％)[1]だが存在したので留意されたい。すなわち，せん妄の病因は複数(例：感染症や電解質異常)あり包括的な対応が必要だが，その1つの選択肢としてフェンタニル注射剤への切り替えを念頭におくべきである。ちなみに，鎮痛状態や全身状態が不安定なときにはフェンタニル貼付剤への切り替えはリスク上も避けたいところである。

2．悪心・嘔吐と便秘

この副作用は，モルヒネ注射剤との差はないとされる。稀ではあるが(各1％)[1]，せん妄と同様に原因検索と対応でも改善が乏しい場合はフェンタニル注射剤への切り替えを考慮する。

3．持続皮下投与における皮膚の発赤・硬結

PAV注での経験であるが，モルヒネ注射剤より若干頻度が高いという印象がある（3％）[1]。薬剤としてのpHに大きな差はなく，混合されているヒドロコタルニンの影響の可能性も否定できない。臨床試験でも35％と高い頻度で発生しているので，注意が必要である。

刺し替えが頻回になると，①患者や看護師の負担になる，②レスキュードーズを遠慮するようになる，③皮膚のアレルギー感作（？）で続行困難になる，などが起こる。よって「軽度のうちに」対応するべきで，特に2週間以上の皮下投与においてはリスクが高いと思われる[1]。よく行われる対策（現場の知恵）であるが，筆者もPAV注を使用する場合生理食塩水による希釈（濃度50％が目安）やステロイド混注（1日量ベタメタゾン1mg前後）を行っており，有用である。しかし，稀ながらモルヒネ注射剤への切り替えを要する症例もあった（3％）[1]。OXJについては，皮下投与の市販後調査が必要だろう。

おわりに

新規のオピオイドが毎年のように市場に登場するが，がん治療に携わる医師は抗がん剤のように「待っていた！」と快哉することは少ないだろう。しかし，図抜けて日本が先進7ヵ国で鎮痛水準指標の麻薬消費量が少ないうえに，2011年からアジアにおいても韓国に抜かれ第2位に転落したことを考えてみてほしい。われわれ医療者は，この事実を真摯に受け止めて，がん患者の除痛率を上げていかねばならない。

今後全国の医療機関で，OXJという選択肢が増えることで1人でも多くの患者が痛みから解放されることを願う。本稿が多少なりともそのヒントとなれば，これにすぎる筆者の喜びはない。

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Review Article

The National Database of Hospital-based Cancer Registries: A Nationwide Infrastructure to Support Evidence-based Cancer Care and Cancer Control Policy in Japan

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Monitoring the current status of cancer care is essential for effective cancer control and high-quality cancer care. To address the information needs of patients and physicians in Japan, hospital-based cancer registries are operated in 397 hospitals designated as cancer care hospitals by the national government. These hospitals collect information on all cancer cases encountered in each hospital according to precisely defined coding rules. The Center for Cancer Control and Information Services at the National Cancer Center supports the management of the hospital-based cancer registry by providing training for tumor registrars and by developing and maintaining the standard software and continuing communication, which includes mailing lists, a customizable web site and site visits. Data from the cancer care hospitals are submitted annually to the Center, compiled, and distributed as the National Cancer Statistics Report. The report reveals the national profiles of patient characteristics, route to discovery, stage distribution, and first-course treatments of the five major cancers in Japan. A system designed to follow up on patient survival will soon be established. Findings from the analyses will reveal characteristics of designated cancer care hospitals nationwide and will show how characteristics of patients with cancer in Japan differ from those of patients with cancer in other countries. The database will provide an infrastructure for future clinical and health services research and will support quality measurement and improvement of cancer care. Researchers and policy-makers in Japan are encouraged to take advantage of this powerful tool to enhance cancer control and their clinical practice.

Key words: cancer registry – data infrastructure – national database – quality of care

INTRODUCTION

Cancer control activities in Japan have accelerated since the enactment of the Cancer Control Act in 2007 (1). To ensure high-quality cancer care nationwide, the government designated 289 hospitals as cancer care hospitals throughout Japan. These hospitals, referred to as Designated Cancer Care Hospitals (DCCHs), function as hubs that support cancer care in the area by providing training to health professionals and highly specialized care to patients (e.g. radiation therapy and palliative care) and by fulfilling the information needs of patients (2).

The DCCHs also play a leading role collecting information on cancer care. As part of the requirement for earning the designation, the hospitals operate hospital-based cancer registries that collect basic information on all new patients with cancer who visited the hospitals (2,3). To properly manage the registry, the hospitals are required to hire one or