Original Article

Clinical Effectiveness of Evidence-based Guidelines for Pain Management of Terminal Cancer Patients in Japan

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Abstract

Background The Japanese Society for Palliative Medicine (JSPM) set guidelines for cancer pain management in 1999. However, the clinical effectiveness of the guidelines has not yet been examined.

Methods Two groups of consecutive patients with cancer admitted to 37 national hospitals (collaborating hospitals for pain management research in Japan) were recruited, one from August to September 1999 (who received the standard treatment in use before the distribution of JSPM guidelines) and the other from July 2000 to May 2001 (who received treatment after the distribution of JSPM guidelines). Demographics, type of cancer and other baseline information were recorded for both groups. In addition, the intensity of pain (evaluated on a 4-level scale of none, mild, moderate, severe; and a visual analog scale of 0 to 100), its duration, source and location were recorded at base line, 1 week and 2 weeks after the start of pain management for two groups and compared by statistical methods.

Results A total of 314 cancer patients received the standard pre-guidelines treatment from August to September 1999 and 106 patients received the post-guidelines treatment from July 2000 to May 2001. No significant differences have been observed between the two groups in terms of baseline characteristics. There were more patients with lung cancer in the pre-guidelines treatment group and more with gastric cancer in the post-guidelines treatment group. More oral opioids ($P = 0.004$) and more adjuvant drugs such as nonsteroidal anti-inflammatory drugs ($P = 0.001$) and hydroxyzine ($P = 0.001$) were used in the post-guidelines treatment group than in the pre-guidelines treatment group and the opposite was true for intravenous ($P = 0.022$) and suppository ($P = 0.041$) opioids. More patients in the post-guidelines treatment group became pain free after 2 weeks compared to those in the pre-guidelines treatment group (14.7% vs. 8.8%) ($P = 0.036$). Moreover, significantly fewer adverse reactions and more recovery from the adverse reactions which did occur were found in the post-

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guidelines treatment group than in the pre-guidelines treatment group.

Conclusion The implementation of JSPM pain management guidelines for cancer patients was effective in increasing the proportion of patients relieved of pain and in reducing adverse reactions to opioids.

Key words Pain management, Japanese Society for Palliative Medicine, Treatment guidelines, Cancer pain, Opioids and non-opioid analgesics, Clinical effectiveness

Introduction

The main goal of palliative care of patients with incurable cancer is to improve their quality of life by managing pain and other symptoms. It has been reported that 70% of all cancer patients suffer from pain[1] and that 36% of those with metastasis have pain severe enough to impair their physical and social functioning.[2] Opioids, the most effective medicine for suppressing pain, often cause adverse reactions such as constipation, nausea/vomiting and drowsiness. This fact raises fear in many cancer patients,[3–5] hindering the adequate use of pain medications including opioids and non-opioid analgesics.[6]

For this reason, the World Health Organization (WHO) developed clinical guidelines for pain and symptom management as a part of palliative care in 1986.[7] The guidelines consist of a three-step "analgesic ladder" approach that was reportedly effective in relieving pain in 69–100% of cancer patients.[8]

However, patient outcomes have not always been consistent and satisfactory. Case series studies, for example, showed that 45–65% of patients with cancer suffered intractable pain[9,10] and over 70% reported at least one symptom during the course of treatment[11] despite the employment of recommended analgesic regimens. Moreover, the validity of studies to assess the effectiveness of WHO guidelines was questioned due to methodological limitation, in particular, the lack of controls for comparison.[8]

In Japan, the Japanese language version of the WHO guidelines has been available since 1987. Although the proportions of complete pain relief among cancer patients in Japan rose from 38% in 1986 to 57% in 1998,[12,13] cancer pain management remains a critical issue in palliative care. To further improve the control of cancer pain, the Japanese Society for Palliative Medicine (JSPM) established guidelines in 1999 based on the best available evidence from scientific studies in and outside of Japan.[14]

We conducted this study to explore the effectiveness of the JSPM guidelines in terms of pain relief, adverse reactions, and quality of life in cancer patients.

Methods

The guidelines

The Evidence-based Cancer Pain Management Guidelines were developed in 1999 by the Guidelines Preparation Committee of the JSPM as described elsewhere.[15] They were formulated in such a manner that the recommended type and dosage of drugs were adapted to local settings in Japan. These JSPM guidelines were distributed in October 1999 to 37 national hospitals throughout the country.

Design and patients

Directors at 37 national hospitals in Japan were invited to participate in this study. These hospitals had already been collaborating in a series of surveys on pain management for cancer patients since 1986. Two groups of consecutive patients with terminal cancer admitted to these hospitals were recruited, one from August to September

1999 (pre-guidelines treatment group) and the other from July 2000 to May 2001 (post-guidelines treatment group). The patients of the pre-guidelines treatment group received pain management before the distribution of the JSPM guidelines and those of the post-guidelines treatment group did so after the distribution of the JSPM guidelines. All patients gave informed consent in writing before participating in this study. Changes in the type and dosage of analgesics, and the management of adverse reactions, if any, were recorded by the physicians in charge of subject patients.

Measurements

At baseline, information on demographics and type of cancer was recorded from medical records. A battery of pain measurement tests were conducted at baseline, 1 week and 2 weeks after the start of pain management by either the pre-guidelines treatment or the post-guidelines treatment. The primary outcome index was the degree of subjective pain in terms of duration and intensity. Intensity was measured by a 4-level scale (none, mild, moderate, or severe) and visual analog scale (VAS) on a 0-to-100 range, with 0 representing no pain and 100 worst pain. The duration was measured as the proportion of the day in which the average and the worst pain were experienced. The source and location of pain were also recorded by attending physicians. The secondary outcomes indices were analgesic dosing and adverse reactions of the analgesics. These data were extracted from medical records.

Statistical analysis

SAS was used for all statistical analyses. Outcome and baseline values for the pre-guidelines treatment group and the post-guidelines treatment group were compared by means of t-tests for continuous variables and of chi-square tests for categorical variables. T-tests were also used to compare changes in scores from the baseline to one week and two weeks for the two groups.

The calculation of sample size was based on a two-tailed t test with a significance level of 0.05, a power level of 0.80, and a clinical effect size of 10 VAS score of average pain reduction and a standard deviation of 25 VAS score from baseline to 2 weeks between the two treatment groups. The required sample size was calculated to be 99 for each group.

Results

Patient characteristics

A total of 420 cancer patients were enrolled in the study; 314 patients received the pre-guidelines treatment from August to September 1999 and 106 patients received the post-guidelines treatment from July 2000 to May 2001. Patient characteristics are shown in Table 1. The mean age was 63 years (range: 7 to 96 years) with men representing 58% of all patients. Underlying diseases were lung cancer (22.3%), colorectal cancer (15.9%), and gastric cancer (10.8%). Patients had an average of two pain locations, a VAS score of 29.8 for the average pain, and a VAS score of 54.0 for the worst pain.

Between the two groups, there were no significant differences in age, sex, baseline VAS for the average pain, baseline VAS for the worst pain, baseline duration of pain, performance status and the ability to ingest orally. However, significant differences were found in the diagnosis and the type of previous treatment aimed at curing the cancer. The number of patients with gastric cancer was significantly greater in the pre-guidelines treatment group than in the post-guidelines treatment group while the number of patients with lung cancer and the proportion of patients who received radiation therapy were significantly greater in the post-guidelines treatment group than in the pre-guidelines treatment group.

Pain assessment

The changes in VAS score for the average and worst pain, duration of the average pain

Table 1 Baseline patient characteristics

	Pre-guidelines treatment group (n=314)	Post-guidelines treatment group (n=106)	Both groups (n=420)	P value
Age, years (SD)	62.6 (12.8)	63.7 (11.6)	62.9 (12.5)	0.20
Sex, %				
Male	57.9	57.7	57.8	1.0
Diagnosis, %				
Lung cancer	19	32.7	22.3	$<0.01^{\dagger}$
Colorectal cancer	17.1	12.1	15.9	0.2
Gastric cancer	12.2	6.5	10.8	$<0.01^{\dagger}$
Breast cancer	9.1	9.3	9.2	1.0
Pancreatic cancer	7.0	5.6	6.7	0.67
Hepatocellular carcinoma	6.1	4.7	5.8	0.58
Others	29.5	29.1	29.3	0.99
Metastasis	86.5	86.4		0.94
Type of treatment				
Operation, %	5.2	1.9	4.4	0.15
Chemotherapy, %	28.1	24.5	27.2	0.48
Radiation, %	24.7	35.8	27.4	$0.03^{\dagger}$
Palliative Care, %	43.6	42.5	43.3	0.83
PS, %				0.89
0–2	51.3	52.0	51.3	
3–4	48.7	48.0	48.7	
Oral ingestion				
Possible, %	80.7	86.5	82.1	0.18

Note: † = $P<0.05$; PS = performance status

Table 2 Pain assessment

	Pre-guidelines treatment group	Post-guidelines treatment group	P value
Duration of pain (SD), hr			
Mean at baseline	6.65 (7.27)	8.63 (8.35)	0.08
1 week after	5.17* (6.23)	5.75* (6.53)	0.56
2 weeks after	4.29* (5.25)	5.54* (6.42)	0.07
0 day–14 days	2.17 (6.21)	2.56 (6.57)	0.64
VAS at usual (SD), mm			
Mean at baseline	29.1 (24.8)	32.1 (24.8)	1.00
1 week after	25.2* (23.5)	27.2* (25.1)	0.43
2 weeks after	22.8* (22.9)	23.5* (23.6)	0.78
0 day–14 days	6.7 (25.6)	9.8 (26.8)	0.33
VAS at worst (SD), mm			
Mean at baseline	55.1 (31.3)	51.0 (30.3)	0.73
1 week after	45.1* (30.6)	42.4* (29.8)	0.77
2 weeks after	39.2* (31.1)	36.2* (29.2)	0.49
0 day–14 days	15.5 (30.6)	15.3 (27.1)	0.94
Duration of sleep (SD), hr			
Mean at baseline	8.05 (5.87)	7.28 (2.56)	0.00
1 week after	7.95 (3.44)	7.92* (2.56)	0.00
2 weeks after	8.17* (4.33)	8.32* (3.53)	0.03
14 days–0 day	0.47 (2.59)	1.05 (3.29)	0.09

*: Statistical comparison was performed between baseline and follow-up points using paired t-test: * = $P<0.05$

Note: 0 day = baseline; 7 days = midpoint; 14 days = endpoint

Mean value baseline minus mean value after 14 days do not correspond exactly to the value in the 0 day–14 days row due to missing data.

Table 3 Prescriptions by physicians

Drug, %	Pre-guidelines treatment group	Post-guidelines treatment group	Both groups	P value
Opioids				
Morphine	71.0	68.9	70.5	0.67
Morphine (p.o.)	12.8	24.5	15.7	<0.01†
Morphine (i.v.)	15.3	6.6	13.2	0.02†
Morphine sulfate (p.o.)	38.7	37.7	38.5	0.86
Morphine (supp.)	12.8	5.7	11.1	0.04†
Pentazocine (p.o.)	8.5	1.9	6.9	0.02†
Pentazocine (i.v.)	1.2	0	0.9	0.25
Buprenorphine (supp.)	1.2	1.9	1.4	0.26
Buprenorphine (i.v)	1.2	0	0.9	0.25
Non-steroidal anti-inflammatory drugs	30.5	50.0	35.2	<0.01†
Diclofenac (supp.)	12.5	23.6	15.2	<0.01†
Loxoprofen (p.o.)	11.9	19.8	13.8	0.04†
Diclofenac (p.o.)	4.9	0.9	3.9	0.07
Others				
Hydroxizine (p.o.)	0.3	4.7	1.4	<0.01†
Prednisolone (i.v.)	0.9	0	0.7	0.32
Imipramine	0.3	0.9	0.5	0.4
Metoclopramide (p.o.)	0	1.9	0.4	0.01†

Note: † = P<0.05; supp. = suppository; p.o. = per os; i.v. = intravenous

and duration of sleep from baseline to 2 weeks were 6.7 VAS score, 15.5 VAS score, 2.17 hr and 0.47 hr in the pre-guidelines treatment group, and 9.8 VAS score, 15.3 VAS score, 2.56 hr and 1.05 hr in the post-guidelines treatment group, respectively, (Table 2) with no significant difference between the two groups. However, both groups showed a steady downward trend during the study period. Patients who allegedly had no pain at baseline due to ongoing therapy accounted for 10.8% in the pre-guidelines treatment group and 11.4% in the post-guidelines treatment group. The proportion of patients free from pain at 2 weeks was 19.6% in the pre-guidelines treatment group and 26.1% in the post-guidelines treatment group. Thus, the proportion of patients who were relieved of pain during the study period was higher in the post-guidelines treatment group compared to that in the pre-guidelines treatment group (14.7% vs. 8.8%, P = 0.036).

Analgesic use

Analgesics used in the study periods are shown in Table 3. Although the total use of morphine did not significantly differ between the two groups, significantly more oral opioids were used in the post-guidelines treatment group than in the pre-guidelines treatment group (P = 0.004) and the opposite was true for intravenous (P = 0.022) and suppository (P = 0.041) opioids. Moreover, significantly more adjuvant drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) (P = 0.001) and hydroxizine (P = 0.001) were used in patients in the post-guidelines treatment group than the pre-guidelines treatment group. The use of tricyclic antidepressants and prednisolone did not significantly differ between the two groups.

Management of adverse reactions

Symptoms of adverse reactions are shown in Table 4. The major adverse reactions to opioids at baseline included constipation (53.3% in the pre-guidelines treatment group; 32.7% in the post-guidelines treatment group), nausea/vomiting (23.2%; 15.4%), and drowsiness (38.7%; 29.8%).

Table 4 Adverse reactions

Adverse reactions	Pre-guidelines treatment group	Post-guidelines treatment group	Both groups	P value
Constipation at baseline, %	53.3	32.7	48.2	<0.01†
Incidence, %	23.1	11.8	19.4	0.05
Cured patients, %	6.4	17.3	9.1	0.02†
Vomiting at baseline, %	23.2	15.4	21.2	0.09
Incidence, %	14.9	5.7	12.4	0.03†
Cured patients	13.2	40.6	20.3	0.01†
Drowsiness at baseline, %	38.7	29.8	36.4	0.11
Incidence, %	26.5	9.5	21.6	<0.01†
Cured patients, %	3.7	19.4	8.0	0.01†

Note: † = $P<0.05$

Significantly fewer adverse reactions occurred in the post-guidelines treatment group than in the pre-guidelines treatment group in terms of nausea/vomiting ($P=0.03$) and drowsiness ($P<0.01$). At the same time, the proportion of patients who recovered from such adverse reactions as constipation ($P=0.02$), nausea/vomiting ($P=0.01$), and drowsiness ($P=0.01$) were significantly greater in the guidelines treatment group than in the pre-guidelines treatment group.

Discussion

Our study showed that more patients in the post-guidelines treatment group became pain free after 2 weeks compared to those in the pre-guidelines treatment group. Moreover, significantly fewer adverse reactions and more recovery from adverse reaction were found in the post-guidelines treatment group than in the pre-guidelines treatment group. However, there was no significant difference in the intensity of the average and the worst pain between the two groups. Contrary to our findings, Du Pen et al. showed in a randomized controlled trial that cancer patients treated in accordance with pain management guidelines had a statistically shorter duration of the average pain, but not of the worst pain, than those treated without guidelines.[16] The lack of significant reduction in pain intensity in the current study could have several reasons. First, adjuvant drugs were not prescribed more frequently in the post-guidelines treatment group than the pre-guidelines treatment group in spite of the recommendation of the use of these drugs in the JSPM guidelines. For example, tricyclic antidepressant drugs are recommended as the first-line adjuvant therapy for neuropathic pain[17,18] and corticosteroids for acute nerve compression, visceral distention and increased intracranial pressure.[19] However, there were no significant differences in the rate of prescriptions of these adjuvant drugs between the two groups. This contrasts with the report by Du Pen et al, in which significantly more tricyclic antidepressants were used in the post-guidelines treatment group than in the pre-guidelines treatment group.[16] In addition to physicians' reluctance to prescribe opioids, which was already shown to be a barrier to adequate cancer pain management,[19,20] a similar reluctance to prescribe antidepressants is likely to be an important factor. Education and training of physicians on the adequate use of antidepressants is mandatory. Second, the observation period of this study was only 2 weeks, much shorter than that of the study by Du Pen et al. which was 3 months.[16]

The current study showed that oral opioids and NSAIDs were prescribed significantly more in the post-guidelines treatment group than in the pre-guidelines treatment group. Similar findings have been reported

from a case series study.[11] In the randomized controlled trial by Du Pen et al, significantly more NSAIDs were prescribed for the guidelines treatment group, although this tendency was not observed for opioids.[16] NSAIDs are generally prescribed for relieving pain of mild to moderate intensity and pain due to bone metastasis[21] and soft-tissue infiltration. This is because these drugs were shown to have not only a fast acting analgesic effect but also an opioid-sparing effect when used as adjuvant drugs.[22] The combination with opioids may well result in a reduction of the dosage of opioids leading to fewer side effects from opioids. For these reasons, a change in physicians' attitude towards increased use of NSAIDs in accordance with the JSPM guidelines should bring benefits to cancer patients.

The most common adverse reactions to the opioids among our patients were constipation, nausea/vomiting, and drowsiness, as reported in previous studies.[4] The proportion of patients who developed such adverse reactions was significantly smaller in the post-guidelines treatment group than in the pre-guidelines treatment group. The JSPM guidelines describe how to prevent adverse reactions to opioids by prescribing prophylactically laxatives and antiemetics from the start of pain management. In fact, several case series showed that adverse reactions to opioids were significantly reduced by following the WHO guidelines.[4,5,11] The current study has confirmed this effectiveness of clinical guidelines in reducing adverse reactions.

There are several limitations to the current study. The major concern is the non-randomized and non-parallel nature of the study design employed, which could result in a measurement bias, since physicians treating patients in the post-guidelines treatment group were not blinded to the use of the guidelines. Furthermore, there might have been a secular trend toward better pain management during the interval of approximately one year between the pre-guidelines treatment group and the post-guidelines treatment group. In addition, the VAS employed here may not be sensitive enough to reflect the complexity of the pain experience in individual patients. Finally, the number of patients (106) in the post-guidelines treatment group was unexpectedly smaller than that (314) in the pre-guidelines treatment group. In spite of these limitations, the current study provides important evidence of the clinical effectiveness of the evidence-based guidelines.

In conclusion, the implementation of JSPM guidelines was effective in increasing the proportion of terminal cancer patients relieved of pain and in reducing adverse reactions to opioids.

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