mechanism of how HFS develops remains unclear. However, a high density of sweat glands and thick stratum corneum might be predisposing factors for development of HFS.[4] Other authors have suggested a direct cytotoxic effect on the acral dermis by the inciting chemotherapeutic agent.[3]

The initial symptoms of HFS include dysesthesia with tingling in the extremities, which can progress to burning, pain with dryness, cracking, desquamation, ulceration, and edema.[2] The National Cancer Institute has a helpful grading system for the severity of HFS.

Treatment of HFS remains challenging as the etiology is poorly understood. Suggested therapies include reducing the chemotherapeutic dose, increasing the interval between cycles, or even halting the chemotherapy itself. Analgesics, topical steroids, systemic steroids, and application of cold packs have been used to help improve symptoms. Aloe vera has been shown in some case reports to improve the symptoms and quality of life.[5] There has been much debate on the use of pyridoxine for HFS, but it has not been shown to prevent or delay the onset of HFS.[6]

In our patient, the use of pregabalin improved his symptoms drastically. Pregabalin is an anticonvulsant widely used, specifically for neuropathic pain secondary to various diseases. Pregabalin exerts its therapeutic effects by binding to voltage-gated calcium channels and decreasing synaptic activities and has been shown to be as or more effective than gabapentin with less adverse effects. There is one case report of the efficacy of pregabalin in the treatment of HFS induced by targeted therapies, specifically dabrafenib.[7] As far as we know, there has been no report on the use of pregabalin in docetaxel-induced HFS. However, pregabalin was shown to ameliorate docetaxel-induced neuropathy in rats.[8] Our patient responded well to pregabalin with improvement in his symptoms and the ability to walk within one week of use. Pregabalin is a viable option to help improve the symptoms and quality of life in patients with chemotherapy-related HFS. However, we need to better understand how pregabalin works in improving HFS symptoms.

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https://doi.org/10.1016/j.jpainsymman.2019.03.005

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Palliative Care Physicians' Practice in the Titration of Parenteral Opioids for Dyspnea in Terminally Ill Cancer Patients: A Nationwide Survey

To the Editor:

Dyspnea is among the most prevalent and distressful symptoms in terminally ill cancer patients.[1,2] Opioids remain the mainstream treatment for dyspnea. In the last phase of life, parenteral routes such as continuous subcutaneous/intravenous administration are frequently used to ensure timely titration and reliable administration in the setting of impaired oral intake and decreased consciousness. Guidelines suggest how to start parenteral opioids,[3] but the evidence is scarce regarding further management. In particular, the following questions remain unanswered. What is the best opioid titration strategy? Does an upper limit of opioids exist for dyspnea? What are the next steps if further opioid titration is considered clinically controversial, if not prohibitory, due to emerging opioid side effects? The lack of evidence can lead to marked treatment variability and inconsistent levels of dyspnea control in the last phase of life.

As the first step toward treatment standardization, it is imperative to understand the current practice of palliative care physicians. The aim of this study was to examine palliative care physicians' overall practice associated with parenteral opioids for dyspnea in

terminally ill cancer patients. Specifically, we aimed to explore how physicians manage dyspnea when further opioid titration for persistent dyspnea is considered clinically controversial due to emerging side effects. We also explored how they would titrate parenteral opioids and if they consider that an upper limit of opioids exists.

Methods

We conducted a cross-sectional survey among palliative care physicians in Japan between September and October 2018. The single inclusion criterion was that all participants were palliative care physicians certified by the Japanese Society for Palliative Medicine. We identified a total of 536 certified physicians from the Society's online registry and sent questionnaires to 268 randomly selected physicians.

Because of the lack of an existing specific questionnaire, we developed an ad hoc questionnaire on the basis of literature reviews,[3–8] pilot testing, and discussion among the authors. The questionnaire included several components of physician-reported practice regarding parenteral opioids for dyspnea at rest in terminally ill cancer patients (defined as those with ECOG performance status = 4, with an estimated prognosis one or two weeks). The first component examined physician-reported practice in a hypothetical scenario where a terminally ill cancer patient continued to suffer severe dyspnea despite titration of continuous administration of parenteral morphine. Further titration would be considered clinically controversial because uncomfortable side effects have developed (no respiratory depression). The response options included the following: 1) adding a small amount of midazolam by continuous administration (e.g., ≤10 mg/day), 2) adding benzodiazepines other than midazolam, 3) titrating morphine further, and 4) switching to another opioid. These were rated on a five-point Likert scale (1 = rarely − 5 = very frequently). The participants were also asked about the starting dose of midazolam for dyspnea which is to be added to parenteral morphine in their usual practice. The second component investigated the participants' specific practice regarding titration of parenteral morphine, such as the timing of reevaluation after the initiation or dose adjustment, intervals of dose adjustment (either increase due to suboptimal relief or decrease due to side effects), and rescue doses and intervals. Third, we investigated the participants' opinion about the presence of the upper limit of morphine for dyspnea above which further titration is deemed ineffective (yes/no), as well as physician-perceived upper limits for both opioid-naïve (mg/day) and opioid-tolerant patients (% increase from the baseline).

Descriptive statistic analyses were conducted using SPSS software (version 25; IBM, Tokyo, Japan). Assuming that 50%−70% of participants would frequently or very frequently perform a certain practice, 143−171 subjects would be sufficient to calculate an accuracy to within a 15% width with 95% CIs. This study was approved by the Institutional Review Board of Konan Hospital.

Results

A total of 189 physicians responded (response rate, 71%).

Practice When Further Titration of Morphine Would Be Considered Clinically Controversial

In a scenario where further titration of morphine for severe dyspnea would be considered clinically controversial, 115 participants (61%; 95% CI, 54−68) reported that they would frequently or very frequently add a small amount of midazolam. Sixty-four (34%; 95% CI, 27−41) participants reported that they would frequently or very frequently add benzodiazepines other than midazolam. By contrast, only 32 (17%; 95% CI, 12−23) and 14 (7%; 95% CI, 4−12) reported that they would frequently or very frequently titrate morphine further and switch to another opioid, respectively (Fig. 1). The median starting dose of midazolam was 10 mg/day (interquartile range [IQR]: 5, 10).

Physician-Reported Practice of Morphine Titration

The participants reported that they would reevaluate dyspnea with a median of 3 (IQR: 1, 6) hours after the initiation or dose adjustment of parenteral morphine. They reported that they would increase morphine with a median interval of 6 (IQR: 3, 12) hours as needed in response to suboptimal relief and decrease morphine with a median interval of 4 (IQR: 2, 8) hours if side effects developed. As for rescue doses, the participants would administer a median of a one-hour (IQR: 1, 1) equivalent dose of morphine, with a median interval of 30 (IQR: 15, 30) minutes as needed.

Physician-Perceived Upper Limits of Opioids for Dyspnea

In total, 67 (35%; 95% CI, 29−43) and 60 (32%; 95% CI, 25−39) physicians agreed that there were upper limits of parenteral opioids for dyspnea above which morphine was deemed ineffective for opioid-naïve and opioid-tolerant patients, respectively. The upper limits of parenteral morphine as perceived by these physicians

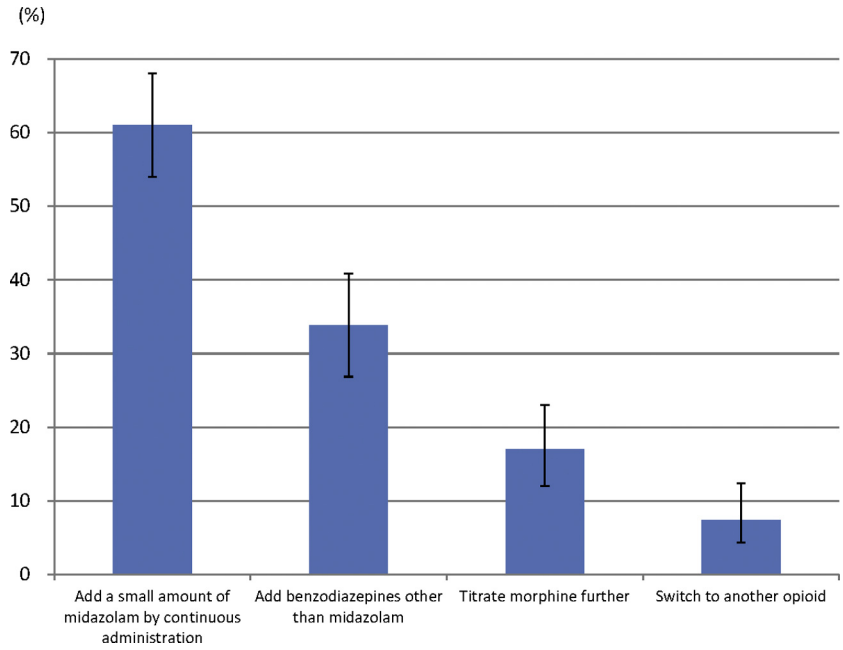

Fig. 1. Rate of physician-reported practice in managing dyspnea when further titration of parenteral morphine is considered clinically controversial ($n = 189$). The bars show the rate (%) of participating physicians who reported that they would frequently or very frequently perform the indicated practice on managing dyspnea when further titration of parenteral morphine is considered clinically controversial.

were medians of 30 mg/day (IQR: 20, 40) and 50% (IQR: 50, 100) increases from the baseline for opioid-naïve and opioid-tolerant patients, respectively.

Discussion

To our knowledge, this is the first nationwide survey among palliative care physicians to investigate their detailed practice in the use of parenteral opioids for dyspnea in terminally ill cancer patients.

The first important finding was that the addition of a small amount of midazolam by continuous administration was the most prevalent practice followed by the regular administration of benzodiazepines other than midazolam when further opioid titration was considered clinically controversial. This is largely consistent with recommendations from previous guidelines,[3,8] although the median dose was lower than that previously reported in clinical trials and guidelines.[3,6] Future studies should explore if the addition of midazolam is truly effective for dyspnea, and if so, the most effective dose.

The second important finding was that approximately a third of physicians agreed that there was an upper limit of opioids for dyspnea in both opioid-naïve and opioid-tolerant patients. The perceived upper limits were relatively low, which was consistent with a previous study in chronic dyspnea which revealed that most dyspnea could be managed with a lower dose of oral morphine (10–30 mg/day).[9] However, the upper limit of opioids for dyspnea in terminally ill cancer patients has not been explored in clinical trials or empirical studies. These findings contrast sharply with pain management in which an upper limit of opioids is widely considered nonexistent. A dose-effect relationship in opioids for dyspnea in terminally ill patients should be investigated in future studies.

The strengths of this study were sampling from the Society's registry of certified palliative care physicians and a relatively high response rate, which ensure generalizability. The limitations included the fact that the questionnaires were not validated and that physician-reported practice might not fully reflect their actual practice. In addition, to maximize a response rate by minimizing participants' burden, we did not obtain detailed demographic data of the participants and achieved the high response rate (71%). Our aim was to explore the overall practice patterns of the board-certified palliative care physicians rather than differences in practice among various subgroups of physicians.

Conclusion

On titrating parenteral opioids for severe dyspnea in terminally ill cancer patients, it was reported that most palliative care physicians would add a small amount of midazolam by continuous administration when further opioid titration is considered clinically

controversial. Future research is warranted to establish a standardized parenteral opioid treatment for dyspnea in terminally ill cancer patients.

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https://doi.org/10.1016/j.jpainsymman.2019.04.007

Disclosures and Acknowledgments

The authors declare no conflict of interest.

This study was in part supported by Grant-in-Aid for Young Scientists of the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Japan Society for the Promotion of Science KAKENHI grant number JP16K15418. The authors would like to thank Drs. Keiko Tanaka and Tatsuya Morita for their valuable advice on their study.

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The Combination of Superior Hypogastric Plexus Block and the Block of the Ganglium Impair in a Patient With Abdominal and Perineal Pain Poorly Responsive to Opioids

Dear Editor,

More than 10 million people worldwide are diagnosed with cancer. About two-thirds of them will experience pain during the course of the disease.[1] The management of cancer pain requires an appropriate multidisciplinary approach involving consideration of the pain's physiopathology, analgesic pharmacology, and the patient's psychosocial concerns. Drug therapy with the use of opioids and adjuvants is successful in 70% to 90% of patients with varied types of cancer pain.[2] Standards for the management of cancer pain have been recently released.[3]

About 10% of patients with cancer pain do not have a good response to drug therapy. An interventional pain treatment may be indicated when drugs do not provide sufficient analgesia or when adverse effects become intolerable.[4] According to recent recommendations of the European Association for Palliative Care, the evidence supporting these procedures is weak for most neurolytic blocks.[5–8] However, in some specific conditions, an interventional approach may produce spectacular improvements