Available evidence shows that the addition of a nonopioid analgesic decreases residual continuous pain in patients receiving only a regular opioid. However, because the analgesic effect of nonopioid analgesics is at most moderate and their long-term use may result in several adverse events, the decision of adding nonopioid analgesics to regular opioid therapy should be made after carefully weighing the benefits of the analgesic effect against the risk of adverse events.

(ii) The dose of regular opioids should be increased in patients who experience continuous pain with regular opioid use. [1B]

Although to date, no clinical trials have compared the amount of increase in regular opioid dose and the interval between increments, several observational studies have demonstrated that the increase strategy based on the WHO method for cancer pain relief provided adequate pain relief (34,35).

Therefore, available evidence suggests that increasing the dose of regular opioids provides pain relief in patients with residual continuous pain despite regular opioid use. When increasing the dose of regular opioids, an increase of 30–50% of the regular daily dose is recommended. However, the total amount of rescue medication required on the previous day must be considered. With regard to the interval between doses, an interval of 24 h for immediate-release opioids or parenteral opioids, 48 h for sustained-release opioids and 72 h for transdermal fentanyl is recommended according to their expected time to achieve steady-state. In cases of severe pain that require prompt analgesia, parenteral opioids or immediate-release opioids are the desirable administration routes.

(iii) The type of opioid should be switched in patients with inadequate pain control with a certain type of opioids. [1B]

A systematic review of 21 observational studies concluded that opioid switching was an effective measure to improve the balance between analgesia and adverse events as a whole (56,57). The studies included in this analysis mainly evaluated the switch from morphine to oxycodone or fentanyl.

Therefore, available evidence suggests that opioid switching could improve analgesic effects and decrease adverse events in cancer patients with inadequate pain control with a certain type of opioid.

(iv) Another type of opioid may be added in patients with inadequate pain control with a certain type of opioid, after consultation with pain or palliative care specialists. [2C]

One observational study evaluating the effectiveness of opioid combination therapy in improving analgesic effects demonstrated that the addition of a second opioid decreased pain intensity without increasing adverse events in cancer patients with inadequate pain control after an increase in the dose of regular opioids (58).

Although the addition of another opioid may provide better analgesic effects in cancer patients with inadequately controlled pain, the present evidence is insufficient. In addition, the concurrent use of different types of opioids may affect compliance. The panel has concluded that after consultation with pain or palliative care specialists, another type of opioid may be added to patients with inadequate pain control with a certain type of opioid.

(v) The administration route may be changed to intravenous or subcutaneous infusion in patients with inadequate pain control with an oral or a transdermal preparation of opioid analgesics. [2C]

Two observational studies evaluating the efficacy of changing to a continuous parenteral route demonstrated that this change decreased pain intensity, decreased adverse events and improved the quality of life in cancer patients with inadequate pain control with oral morphine or transdermal fentanyl (59,60).

Therefore, changing to a parenteral route may facilitate an improvement in the analgesic effect in cancer patients with inadequate pain control with oral or transdermal opioids.

(vi) Ketamine may be used in combination with opioids in patients with inadequately controlled pain after a sufficient increase in opioid dose, after consultation with pain or palliative care specialists. [2B]

A systematic qualitative review including two randomized controlled trials to evaluate the efficacy of ketamine provided a modest conclusion that ketamine had a potential efficacy when used as an adjuvant to opioids for cancer pain (61).

Although the use of ketamine as an adjuvant to opioids may provide better analgesic effects in cancer patients with inadequately controlled pain after a sufficient increase in opioid dose, the present evidence is insufficient. In addition, using ketamine may increase central nervous system (CNS) side effects. The panel has concluded that, after consultation with pain or palliative care specialists, ketamine may be added in patients with inadequately controlled pain after a sufficient increase in opioid dose.

(vii) Corticosteroids may be used in combination with opioids for particular pain etiologies, paying careful attention to the risk of adverse reactions in patients who experience pain after a sufficient increase in opioid dose. [2C]

A small, randomized controlled crossover trial demonstrated that pain intensity in patients with advanced cancer decreased after the administration of methylprednisolone with weak opioids (62). On the other hand, another randomized controlled trial demonstrated that, whereas dexamethasone provided a short-term benefit for gastrointestinal adverse events and improved a patient's sense of well-being, pain intensity was not significantly different between dexamethasone–opioid combination therapy and opioid monotherapy in cancer patients with moderate-to-severe pain (63).

Therefore, there is insufficient evidence for the efficacy of corticosteroids in combination with opioids. However, corticosteroids are considered to decrease the intensity of pain caused by a specific etiology such as spinal cord compression, inflammation, increased intracranial pressure and bone metastasis. Corticosteroids can be used in combination with opioids for pain caused by such etiologies if careful attention is paid to adverse events from long-term corticosteroid use (e.g. hyperglycemia, peptic ulcer, immune suppression, Cushing's syndrome, etc.). Corticosteroids should be continued at the minimum effective dose, and should be tapered and discontinued, when ineffective.

Patients with Breakthrough Pain

(i) The rescue dose of opioids should be used in patients with breakthrough pain. [1B]
(ii) The rescue dose may be increased if adverse events are acceptable and the initial rescue dose provide inadequate analgesic effects. [2C]

Although a Cochrane review on the management of breakthrough pain concluded that a rescue dose was effective for such pain, this systematic review primarily analyzed studies of oral transmucosal fentanyl citrate, which is not available in Japan (64). Although randomized placebo-controlled trials to evaluate the efficacy of oral and parenteral opioids are lacking, there are three observational studies evaluating the efficacy of a rescue dose of subcutaneous or intravenous opioids for breakthrough pain, and two randomized controlled trials of oral transmucosal fentanyl citrate that used oral and intravenous opioids as a control treatment (65–69).

A sub-analysis of a rescue dose of oral morphine in a randomized controlled trial demonstrated that immediate-release morphine caused a clinically significant decrease in breakthrough pain, and the mean intensity of pain decreased 60 min after administration (65). Two observational studies and a sub-analysis of a rescue dose of intravenous morphine in a randomized, controlled trial demonstrated that intravenous morphine caused a clinically significant improvement of breakthrough pain in a majority of patients (66–68). An observational trial demonstrated that subcutaneous morphine relieved breakthrough pain within 10 min in a majority of patients (69). In these studies, serious adverse events were rare.

Therefore, available evidence suggests that using a rescue dose ameliorates breakthrough pain in cancer patients receiving regular opioid doses.

The dosage used in current studies corresponded to 10–20% of the daily regular opioid dose, regardless of the administration route. These trial results suggest that this dose is safe and effective, and the panel has agreed that the starting dose of a rescue opioid should be 10–20% of the daily regular opioid dose when oral immediate-release opioids are used. On the other hand, for patients on continuous parenteral opioids, a 1 h bolus dose of regular parenteral opioid is traditionally used in Japan; therefore, the panel has recommended the 1 h bolus administration in patients on continuous parenteral opioids.

A clinical trial showed that an adequate dose of the rescue opioid would not be completely correlated with the total daily dose of regular opioids (65). Therefore, the panel has agreed that the dosage of the rescue opioid should be increased and adjusted individually if adverse events are acceptable and the initial dose provides inadequate analgesic effects.

(iii) For patients with 'end-of-dose failure,' the dose of regular opioids should be increased or the interval of regular opioid administration should be shortened [1B]

A small, randomized controlled trial comparing the effects of a dose of immediate-release morphine administered every 4 h with those of a bedtime double dose demonstrated that the pain intensity at night and the next morning as well as the requirement of a rescue opioid at night were significantly lower in the 4-h group (70). On the other hand, a small, randomized controlled trial comparing the same groups demonstrated that the pain intensity was not significantly different between the groups (71).

Although available evidence is insufficient to conclude whether an increase in the dose of regular opioids or shortening the dosing interval of regular opioids is appropriate to ameliorate 'end-of-dose failure,' the panel agreed that both the strategies can be used in cancer patients with 'end-of-dose failure' who are using regular immediate-release opioids.

There are no trials evaluating the efficacy of these 2 strategies in patients using regular sustained-release opioids. However, an increase in the dose of regular opioids presumably maintains effective blood concentration and improves 'end-of-dose failure' in patients using regular sustained-release opioids because of their prolonged duration of action. Therefore, the dose of regular opioids can be increased in cancer patients with 'end-of-dose failure' who are using regular sustained-release opioids. The dosing interval can be shortened when an increase in the dose of regular opioids is not effective or causes an adverse event.

Neuropathic Pain in Cancer Patients

(i) Adjuvant analgesics (e.g. anticonvulsants, antidepressants, antiarrhythmics, *N*-methyl-D-aspartate (NMDA) receptor antagonist or corticosteroids) may be used in cancer patients with neuropathic pain. [2B]

(a) Anticonvulsants

Two randomized, controlled trials evaluating the efficacy of gabapentin in cancer patients with neuropathic pain demonstrated that gabapentin as an adjuvant to opioids demonstrated a significantly better analgesic effect against neuropathic pain compared with placebo (72,73). Drowsiness was more frequent in the gabapentin group in both the studies. Also, in noncancer patients, a recent Cochrane systematic review concluded that gabapentin demonstrated a moderate analgesic

effect against neuropathic pain, with adverse effects such as dizziness, drowsiness and headache (74). Other than gabapentin, a randomized controlled trial comparing three arms (buprenorphine alone, phenytoin alone or buprenorphine and phenytoin) did not show any difference in analgesic effect among the three arms in cancer patients with neuropathic pain (75). A small, observational trial evaluating the efficacy of valproate as an adjuvant to opioids in cancer patients with neuropathic pain demonstrated that 56% patients exhibited a decrease in pain intensity (76). Another small, observational trial evaluating the efficacy of clonazepam as an adjuvant to opioids in cancer patients with neuropathic pain demonstrated that although the mean pain intensity decreased from three to one in five patients who completed the study protocol, another five patients dropped out because of worsening pain or drowsiness (77).

Therefore, available evidence suggests that gabapentin improves neuropathic pain in cancer patients. Although some other anticonvulsants may improve neuropathic pain in cancer patients, current evidence for the efficacy of these agents is insufficient.

(b) Antidepressants

A randomized controlled, crossover trial comparing the efficacy of amitriptyline, a tricyclic antidepressant (TCA), as an adjuvant to opioids with that of placebo in cancer patients with neuropathic pain showed that amitriptyline caused a small but significant improvement in maximum pain intensity (78). However, the incidence of adverse effects, such as drowsiness, confusion and dry mouth, was also significantly higher with amitriptyline. In noncancer patients, a recent Cochrane systematic review concluded that TCAs and venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), are effective for achieving at least moderate pain relief in patients with neuropathic pain (79).

Although available evidence is insufficient to establish the efficacy of antidepressants in cancer patients with neuropathic pain, on the basis of data from patients without cancer, TCAs and SNRIs can be used as an adjuvant to opioids in cancer patients with neuropathic pain.

(c) Antiarrhythmics

A randomized, controlled trial evaluating the efficacy of lidocaine (2 mg/kg by bolus infusion followed by a 2 mg/kg drip infusion for 1 h) for the treatment of opioid-refractory neuropathic and other types of pain in cancer patients demonstrated that lidocaine provided a significantly better analgesic effect compared with placebo, with minor adverse effects such as tinnitus and perioral numbness (80). In contrast, two small, randomized controlled, crossover trials evaluating the efficacy of lidocaine in cancer patients with neuropathic pain demonstrated no significant analgesic effect (81,82).

In noncancer patients, a recent Cochrane systematic review concluded that lidocaine and other oral analogs demonstrated better analgesic effects in cancer patients with neuropathic pain compared with placebo, and were as effective as other analgesics (83).

Although the results of available evidence are conflicting and insufficient, the panel concluded that, on the basis of data from patients without cancer, antiarrhythmics may be used as adjuvants to opioids in cancer patients with neuropathic pain.

(d) NMDA receptor antagonists

A small, randomized, controlled, crossover trial evaluating the efficacy of ketamine against opioid-refractory neuropathic or mixed pain in cancer patients demonstrated that ketamine demonstrated a significantly better analgesic effect compared with placebo, with moderate adverse effects such as hallucination and sensation of insobriety (84). In two other small observational studies, ketamine demonstrated a clinically significant decrease in opioid-refractory neuropathic pain in 61–77% patients with cancer (85,86).

Although available evidence is insufficient and there is a well-documented risk of a CNS adverse effect, ketamine may be used as an adjuvant to opioids in cancer patients with opioid-refractory neuropathic pain.

(e) Corticosteroids

Although to date, no clinical trials have evaluated the efficacy of corticosteroids in the treatment of neuropathic pain in cancer patients, corticosteroids are considered to improve the intensity of pain caused by a specific etiology such as spinal cord compression, nerve compression or inflammation.

The panel agreed that corticosteroids can be used as an adjuvant to opioids for neuropathic pain caused by spinal cord compression, other nerve compression by tumor invasion or inflammation in the nervous system.

DISCUSSION

We reported the summary of recommendations of a new Japanese clinical guideline for the management of cancer pain. Although we used a formal evidence-based methodology for constructing this clinical guideline, a majority of the recommendations are based on poor-quality controlled trials, observational studies or expert opinions. This finding confirms that a worldwide effort for conducting well-designed, controlled trials is essential for improving the clinical guideline and management of cancer pain. During our efforts, the European Association of Palliative Care guideline was recently published (16). In this guideline, the key messages and recommendations are essentially the same as in the Japanese guideline; but their recommendation levels are generally weak because of the lack of confirmatory evidence in the majority of fields. The results highlight the importance of conducting well-designed, controlled trials to identify the best practice in cancer pain management.

Conflict of interest statement

None declared.

References

1. Takashi Yamaguchi, Minoru Narita, Tatsuya Morita, Yoshiyuki Kizawa, Motohiro Matoba. Recent developments in the management of cancer pain in Japan: education, clinical guidelines, and basic researches. *Jpn J Clin Oncol* 2012;42:1120–7.
2. Teunissen SCCM, Wesker W, Kruitwagen C, de Haes HCJM, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. *J Pain Symptom Manage* 2007;34:94–104.
3. van den Beuken-van Everdingen M, de Rijke J, Kessels A, Schouten H, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol* 2007;18:1437–49.
4. Deandrea S, Montanari M, Moja L, et al. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol* 2008; 19:1985–91.
5. Yamagishi A, Morita T, Miyashita M, et al. Pain intensity, quality of life, quality of palliative care, and satisfaction in outpatients with metastatic or recurrent cancer: a Japanese, nationwide, region-based, multicenter survey. *J Pain Symptom Manage* 2012;43:503–14.
6. Morita T, Fujimoto K, Namba M, et al. Palliative care needs of cancer outpatients receiving chemotherapy: an audit of a clinical screening project. *Support Care Cancer* 2007;16:101–7.
7. Yamagishi A, Morita T, Miyashita M, Kimura F. Symptom prevalence and longitudinal follow-up in cancer outpatients receiving chemotherapy. *J Pain Symptom Manage* 2009;37:823–30.
8. Cherny N, Ripamonti C, Pereira J, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. *J Clin Oncol* 2001;19:2542–54.
9. Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001;84: 587–93.
10. Jost L. Management of cancer pain: ESMO clinical recommendations. *Ann Oncol* 2007;18:ii92–4.
11. Kvale PA, Selecky PA, Prakash UBS. Palliative care in lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:368S–403S.
12. Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain. *Cancer* 2002;94:832–9.
13. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology, Adult Cancer Pain. http://www.nccn.org/professionals/physician_gls/PDF/pain.pdf
14. Japanese Society for Palliative Medicine. The evidence-based medicine-supported cancer pain management guideline. Shinko Trading Co Ltd. 2000. (in Japanese).
15. Guyatt GH, Oxman AD, Visit GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
16. Caraceni A, Hanks G, Kaasa S, et al. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. *Lancet Oncol* 2012;13:e58–68.
17. Leser JD, Butler SH, Chapman CR, Turk DC, editors. *Bonica's Management of Pain*, 3rd ed. Lippincott Williams & Wilkins, 2001.
18. Berger AM, Shuster JL, Von Roenn JH, editors. *Principles and Practice of Palliative Care and Supportive Oncology*, 3rd ed. Lippincott Williams & Wilkins, a Wolters Kluwer Business, 2007.
19. Doyle D, Hanks GWC, Cherny NI, Calman K, editors. *Oxford Textbook of Palliative Medicine*, 3rd ed. Oxford University Press, 2005.
20. McMahon SB, Koltzenburg M, editors. *Wall and Melzack's Textbook of Pain*, 5th ed. Elsevier Churchill Livingstone, 2006.
21. Walsh D, editors. *Palliative Medicine*. Saunders Elsevier, 2009.
22. Bruera E, Higginson IJ, Ripamonti C, von Gunten C, editors. *Textbook of Palliative Medicine*. London: Hodder Arnold, 2006.
23. Fitch K, Bernstein SJ, Aguilar MD, et al. *The Rand/UCLA Appropriateness Method User's manual*. Santa Monica, CA: RAND, 2001.
24. Stambaugh JE, Jr. Additive analgesia of oral butorphanol/acetaminophen in patients with pain due to metastatic carcinoma. *Curr Ther Res* 1982;31:386–92.
25. McNicol E, Strassels SA, Goudas L, et al. NSAIDS or paracetamol, alone or combined with opioids, for cancer pain. *Cochrane Database Syst Rev* 2005;Jan 25;(1):CD005180.
26. Moertel CG, Ahmann DL, Tylor WF, et al. Aspirin and pancreatic cancer pain. *Gastroenterology* 1971;60:552–3.
27. Moertel CG, Ahmann DL, Tylor WF, et al. Relief of pain by oral medications. A controlled evaluation of analgesic combinations. *JAMA* 1974;229:55–9.
28. Stambaugh JE, Jr, Drew J. A double-blind parallel evaluation of the efficacy and safety of single dose of ketoprofen in cancer pain. *J Clin Pharmacol* 1988;28:S34–9.
29. Saxena A, Andley M, Gnanasekaran N. comparison of piroxicam and acetylsalicylic acid for pain in head and neck cancers: a double-blind study. *Palliat Med* 1994;8:223–9.
30. Turnbull R, Hills LJ. Naproxen versus aspirin as analgesics in advanced malignant disease. *J Palliat Care* 1986;1:25–8.
31. Ventafridda V, Toscani F, Tamburini M, et al. Sodium naproxen versus sodium diclofenac in cancer pain control. *Arzneimittelforschung* 1990; 40:1132–4.
32. Ventafridda V, de Conno F, Panerai AE, et al. Non-steroidal anti-inflammatory drugs as the first step in cancer pain therapy: double-blind, within-patient study comparing nine drugs. *J Int Med Res* 1990;18:21–9.
33. Evidence-based Gastric Ulcer Treatment Guideline Committee. *Evidence-based Gastric Ulcer Treatment Guideline*. 2nd ed. Jihou, 2007. (in Japanese).
34. Ventafridda V, Tamburini M, Caraceni A, et al. Validation study of the WHO method for cancer pain relief. *Cancer* 1987;59:850–6.
35. Azevedo Sao Leao Ferreira K, Kimura M, Jacobsen Teixeira M. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? *Support Care Cancer* 2006;14:1086–93.
36. Marinangeli F, Ciccozzi A, Leonardis M, et al. Use of strong opioids in advanced cancer pain: a randomized trial. *J Pain Symptom Manage* 2004;27:409–16.
37. Maltoni M, Scarpi E, Modonesi C, et al. A validation study of the WHO analgesic ladder: a two-step vs three-step strategy. *Support Care Cancer* 2005;13:888–94.
38. Wiffen PJ, McQuay HJ. Oral morphine for cancer pain. *Cochrane Database Syst Rev* 2007;Oct 17;(4):CD003868.
39. Silvestri B, Bandieri E, Del Prete S, et al. Oxycodone controlled-release as first-choice therapy for moderate-to-severe cancer pain in Italian patients: results of an open-label, multicentre, observational study. *Clin Drug Investig* 2008;28:399–407.
40. Reid CM, Martin RM, Sterne JA, et al. Oxycodone for cancer-related pain: meta-analysis of randomized controlled trials. *Arch Intern Med* 2006;166:837–43.
41. Lauretti GR, Oliveira GM, Pereira NL. Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients. *Br J Cancer* 2003;89:2027–30.
42. Wong JO, Chiu GL, Tsao CJ, Chang CL. Comparison of oral controlled-release morphine with transdermal fentanyl in terminal cancer pain. *Acta Anesthesiol Sin* 1997;35:25–32.
43. Kress HG, Von der Laage D, Hoerauf KH, et al. A randomized, open, parallel group, multicenter trial to investigate analgesic efficacy and safety of a new transdermal fentanyl patch compared to standard opioid treatment in cancer pain. *J Pain Symptom Manage* 2008;36:268–79.
44. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. *J Pain Symptom Manage* 1997;13:254–61.
45. Hunt R, Fazekas B, Thorne D, Brooksbank M. A comparison of subcutaneous morphine and fentanyl in hospice cancer patients. *J Pain Symptom Manage* 1999;18:111–9.
46. Mystakidou K, Tsilika E, Parpa E, et al. Long-term cancer pain management in morphine pre-treated and opioid naive patients with transdermal fentanyl. *Int J Cancer* 2003;107:486–92.
47. Vielvoye-Kerkmeer AP, Mattern C, Uitendaal MP. Transdermal fentanyl in opioid-naive cancer pain patients: an open trial using transdermal fentanyl for the treatment of chronic cancer pain in opioid-naive patients and a group using codeine. *J Pain Symptom Manage* 2000;19:185–92.
48. van Seventer R, Smit JM, Schipper RM, et al. Comparison of TTS-fentanyl with sustained-release oral morphine in the treatment of patients not using opioids for mild-to-moderate pain. *Curr Med Res Opin* 2003;19:457–69.

49. Dean M. Opioids in renal failure and dialysis patients. *J Pain Symptom Manage* 2004;28:497–504.
50. Ben-Ahron I, Gafter-Gvil A, Paul M, et al. Interventions for alleviating cancer-related dyspnea: a systematic review. *J Clin Oncol* 2008;26:2396–404.
51. Stambaugh JE, Reder RF, Stambaugh MD, et al. Double-blinded, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. *J Clin Pharmacol* 2001;41:500–6.
52. Stambaugh JE, Jr, Drew J. The combination of ibuprofen and oxycodone/acetaminophen in the management of chronic cancer pain. *Clin Pharmacol Ther* 1988;44:665–9.
53. Bjorkman R, Ullman A, Hedner J. Morphine-sparing effect of diclofenac in cancer pain. *Eur J Clin Pharmacol* 1993;44:1–5.
54. Mercadante S, Fulfaro F, Casuccio A. A randomised controlled study on the use of anti-inflammatory drugs in patients with cancer pain on morphine therapy: effects on dose-escalation and a pharmacoeconomic analysis. *Eur J Cancer* 2002;38:1358–63.
55. Stockler M, Vardy J, Pillai A, et al. Acetaminophen (paracetamol) improves pain and well-being in people with advanced cancer already receiving a strong opioid regimen: a randomized, double-blind, placebo-controlled cross-over trial. *J Clin Oncol* 2004;22:3389–94.
56. Quigley C. Opioid switching to improve pain relief and drug tolerability. *Cochrane Database Syst Rev*. 2004;CD004847.
57. Mercadante S, Bruera E. Opioid switching: a systematic and critical review. *Cancer Treat Rev* 2006;32:304–15.
58. Mercadante S, Villari P, Ferrera P, et al. Addition of another opioid may improve opioid response in cancer pain: preliminary data. *Support Care Cancer* 2004;12:762–6.
59. Drexel H, Dzien A, Spiegel RW, et al. Treatment of severe cancer pain by low-dose continuous subcutaneous morphine. *Pain* 1989;36:169–76.
60. Enting RH, Oldenmenger WH, van der Rijt CC, et al. A prospective study evaluating the response of patients with unrelieved cancer pain to parenteral opioids. *Cancer* 2002;94:3049–56.
61. Bell R, Eccleston C, Kalso E. Ketamine as an adjuvant to opioids for cancer pain. *J Pain Symptom Manage* 2003;26:867–75.
62. Bruera E, Roca E, Cedaro L, et al. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep* 1985;69:751–4.
63. Mercadante SL, Berchovich M, Casuccio A, et al. A prospective randomized study of corticosteroids as adjuvant drugs to opioids in advanced cancer patients. *Am J Hosp Palliat Care* 2007;24:13–9.
64. Zeppetella G, Ribeiro MD. Opioids for the management of breakthrough (episodic) pain in cancer patients. *Cochrane Database Syst Rev* 2006;CD004311.
65. Coluzzi PH, Schwartzberg L, Conroy JD, Jr, et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC (R)) and morphine sulfate immediate release (MSIR (R)). *Pain* 2001;91:123–30.
66. Mercadante S, Villari P, Ferrera P, et al. Safety and effectiveness of intravenous morphine for episodic (breakthrough) pain using a fixed ratio with the oral daily morphine dose. *J Pain Symptom Manage* 2004;27:352–9.
67. Mercadante S, Intravaia G, Villari P, et al. Intravenous morphine for breakthrough (episodic-) pain in an acute palliative care unit: a confirmatory study. *J Pain Symptom Manage* 2008;35:307–13.
68. Mercadante S, Villari P, Ferrera P, et al. Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic breakthrough pain. *Br J Cancer* 2007;96:1828–33.
69. Enting RH, Mucchiano C, Okdenmenger WH, et al. The 'pain pen' for breakthrough cancer pain: a promising treatment. *J Pain Symptom Manage* 2005;29:213–7.
70. Tod J, Rees E, Gwilliam B, et al. An assessment of the efficacy and tolerability of a 'double dose'of normal-release morphine sulphate at bedtime. *Palliat Med* 2002;16:507–12.
71. Dale O, Piribauer M, Kaasa S, et al. A double-blind, randomized, crossover comparison between single-dose and double-dose immediate-release oral morphine at bedtime in cancer patients. *J Pain Symptom Manage* 2009;37:68–76.
72. Caraceni A, Zecca E, Bonezzi C, et al. Gabapentin for neuropathic cancer pain: a randomized controlled trial from the gabapentin cancer pain study group. *J Clin Oncol* 2004;22:2909–17.
73. Keskinbora K, Pekel AF, Aydinli I, et al. Gabapentin and an opioid combination versus opioid alone for the management of neuropathic cancer pain: a randomized open trial. *J Pain Symptom Manage* 2007;34:183–9.
74. Wiffen PJ, McQuay HJ, Moore RA, et al. Gabapentin for acute and chronic pain. *Cochrane Database Syst Rev* 2005;Jul 20;(3):CD005452.
75. Yajnik S, Singh GP, Singh G, Kumar M. Phenytoin as a coanalgesic in cancer pain. *J Pain Symptom Manage* 1992;7:209–13.
76. Hardy JR, Rees EAJ, Gwilliam B, Ling J. A phase ? study to establish the efficacy and toxicity of sodium valproate in patients with cancer-related neuropathic pain. *J Pain Symptom Manage* 2001;21:204–9.
77. Hugel H, Ellershaw JE, Dickman A. Clonazepam as an adjuvant analgesic in patients with cancer-related neuropathic pain. *J Pain Symptom Manage* 2003;26:1073–4.
78. Mercadante S, Arcuri E, Tirelli W. Amitriptyline in neuropathic cancer pain in patients on morphine therapy: a randomized placebo-controlled, double-blind crossover study. *Tumori* 2002;88:239–42.
79. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev* 2007;Oct 17;(4):CD005454.
80. Sharma S, Rajagopal MR, Palat G, et al. A phase ? pilot study to evaluate use of intravenous lidocaine for opioid-refractory pain in cancer patients. *J Pain Symptom Manage* 2009;37:85–93.
81. Ellemann K, Sjogren P, Banning AM, et al. Trial of intravenous lidocaine on painful neuropathy in cancer patients. *Clin J Pain* 1989;5:291–4.
82. Bruera E, Ripamonti C, Brenneis C, et al. A randomized double-blind crossover trial of intravenous lidocaine in the treatment of neuropathic cancer pain. *J Pain Symptom Manage* 1992;7:138–40.
83. Challapalli V, Tremont-Lukats IW, McNicol ED, et al. Systemic administration of local anesthetic agents to relieve pain. *Cochrane Database Syst Rev* 2005;Oct 19;(14):CD003345.
84. Mercadante S, Arcuri E, Tirelli W, et al. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage* 2000;20:246–51.
85. Jackson K, Ashby M, Martin P, et al. 'Burst' ketamine for refractory cancer pain: an open-label audit of 39 patients. *J Pain Symptom Manage* 2001;22:834–42.
86. Kannan TR, Saxena A, Bhatnagar S, et al. Oral ketamine as an adjuvant to oral morphine for neuropathic pain in cancer patients. *J Pain Symptom Manage* 2002;23:60–5.

APPENDIX

MEMBERS OF THE TASK GROUP FOR THE CLINICAL GUIDELINE FOR CANCER PAIN MANAGEMENT

Yasuo Shima: Department of Palliative Medicine, Tsukuba Medical Center Hospital; Miki Hosoya: Department of Nursing, National Cancer Center; Motohiro Matoba: Department of Palliative Medicine/Psycho-oncology Division, National Cancer Center; Tatsuya Morita: Department of Palliative and Supportive Care, Seirei Mikatahara General Hospital; Toru Akagi: Department of Pharmacy, National Cancer Center; Yasuaki Arai: Department of Diagnostic Radiology, National Cancer Center; Tomoko Arahata: Faculty of Nursing and Medical Care, Keio University; Etsuko Aruga: Department of Internal Medicine/Division of Palliative Medicine, Teikyo University School of Medicine; Masayuki Ikenaga: Hospice, Yodogawa Christian Hospital; Tomoko Izawa: Department of Nursing, Kyoto University Hospital; Yuya Ise: Department of Pharmacy, Nippon Medical School Hospital; Masako Iseki: Department of Anesthesiology and Pain Management, Juntendo University School of Medicine; Toshimasa Itoh: Department of Pharmacy, Tokyo Women's Medical University Hospital; Noriko Iba: DIPEx-Japan; Kengo Imai: Hospice, Yodogawa Christian Hospital; Yasuhito Uezono: Division of Cancer

Pathophysiology, National Cancer Center Research Institute; Keiko Ueda: Department of Palliative Care, Keiyukai Sapporo Hospital; Megumi Umeda: Palliative Care Partners Co.,ltd.; Iwao Osaka: Department of Palliative Medicine, Shizuoka Cancer Center; Masahiro Osawa: Department of Pathophysiology and Therapeutics, Hoshi University School of Pharmacy and Pharmaceutical Sciences; Misato Ohata: Department of Nursing, St.Luke's International Hospital; Rie Ogasawara: Department of Nursing, Yokohama City Minato Red Cross Hospital; Yoshiaki Okamoto: Faculty of Clinical Pharmacy Research and Education/Pharmaceutical Research Center, Osaka University graduate school of pharmaceutical sciences; Teruo Okutsu: Department of Palliative Medicine, Shizuoka Cancer Center; Yukako Okude: Department of Nursing, Juntendo University Hospital; Hajime Kagaya: Department of Pharmacy, Saiseikai Yokohamashi Nanbu Hospital; Ikuko Kazama: Department of Nursing, International University of Health and Welfare Mita Hospital; Shiro Katayama: Department of Pharmacy, Nippon Medical School Hospital; Megumi Kato: Department of Nursing, Japanese Red Cross Musashino Hospital; Kanako Kawachi: Department of Nursing, The Cancer Institute Hospital Of JFCR; Mikiko Kawamura: School of Nursing and Social Services, Health Sciences University of Hokkaido; Hiroya Kinoshita: Department of Palliative Medicine and Psycho-oncology, National Cancer Center Hospital East; Naoko Kuzumaki: Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences; Naoko Kudo: National Cancer Center Research Institute; Hideya Kokubun: Department of Pharmacy, Kitasato University Hospital; Keiko Kojima: Department of Anesthesiology, Jikei University Hospital; Hiroyuki Kohara: Department of Palliative Care, Hiroshima Prefectural Hospital; Sachiko Komiya: Department of Pharmacy, Yokohama City University Hospital; Hiroshi Koyama: Department of Education, National Hospital Organization Kyoto Medical Center; Fumiko Koyama: Department of Nursing, Kinki University Hospital; Tetsuya Sakai: Department of Anesthesiology, Nagasaki University School of Medicine; Atsuko Sakamoto: Department of Nursing, Kyorin University Hospital; Masaki Sakamoto: Department of Palliative Care, Nagoya City University Hospital; Satomi Sasaki: Midori Medical Clinic; Motohiko Sano: Department of Pharmacy Services, Saitama Medical University Saitama Medical Center; Mitsuru Shiokawa: Department of Pharmacy, St.Luke's International Hospital; Satoru Shikata: Department of Surgery, Soseikai General Hospital; Hideki Shishido: Shishido Internal Medicine Clinic; Michihiro Shino: Department of Pharmacy, Shizuoka Cancer Center; Akiko Shinohara: Department of Palliative Medicine, Teikyo University Hospital; Wakako Shimizu: Department of Radiation Oncology, kimitsu Chuo Hospital; Yutaka Shirahige: Shirahige Clinic; Fumiko Shinkai: Department of Nursing, Aichi Cancer Center; Takuya Shinjo: Palliative Care Unit, Shakaihoken Kobe Central Hospital; Akihiko Suga: Department of Palliative Medicine, Shizuoka Saiseikai General Hospital; Tsutomu Suzuki: Department of Toxicology, Hoshi University School of Pharmacy and Pharmaceutical Sciences; Hisamitsu Takase: Department of Pharmacy, Fukuoka University Hospital; Shin'ya Takada: Department of Pharmacy, National Hospital Organization Hokkaido Cancer Center; Masafumi Takada: Department of Anesthesiology, Nagasaki University Hospital; Chizuko Takigawa: Department of Palliative Care, KKR Sapporo Medical Center; Yoshiko Taguchi: Department of Nursing, Osaka Medical Center for Cancer and Cardiovascular Diseases; Keiko Tanaka: Department of Palliative Care, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital; Misuzu Cho: Department of Palliative Care, St.Luke's International Hospital; Kenkichi Tsuruga: Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine; Shiro Tomiyasu: Department of Anesthesiology/Palliative Care Team, Nagasaki Municipal Hospital; Takayuki Nakagawa: Department of Molecular Pharmacology, Graduate School of Pharmaceutical Sciences, Kyoto University; Mari Nakanishi: Nursing Home and Research Center, LLP Expert Home Nursing Systems Japan; Minoru Narita: Department of Pharmacology, Hoshi University School of Pharmacy and Pharmaceutical Sciences; Hiroaki Nishioka: Department of General Internal Medicine, Nagoya Memorial Hospital; Seiichi Nose: Department of Pharmacy, Nagasaki University Hospital; Jun Hamano: Yamato Clinic; Akitoshi Hayashi: Department of Palliative Care, St.Luke's International Hospital; Eriko Hayashi: Department of Nursing, Fujisawa Shounandai Hospital; Takayuki Hisanaga: Department of Palliative Medicine, Tsukuba Medical Center Hospital; Ko Hisahara: Palliative Care Team, Teine Keijinkai Hospital; Seiji Bito: Division of Clinical Epidemiology, National Hospital Organization Tokyo Medical Center; Kayo Hirooka: Research Center for Development of Nursing Practice, St.Luke's College of Nursing; Misako Fukawa: Department of Pharmacy, Kitasato University Hospital; Minoru Hojo: Department of Anesthesiology/Palliative Care Team, Nagasaki University Hospital; Toyoshi Hosokawa: Department of Pain Management and Palliative Care Medicine, Kyoto Prefectural University of Medicine; Osamu Hosoya: Department of Pharmaceutics, Josai University Faculty of Pharmaceutical Sciences; Akiko Honda: Research Center for Development of Nursing Practice, St.Luke's College of Nursing; Naomi Maehori: Lemon Pharmacy, Leben plan Co.,ltd. Mikatahara Branch; Suguru Matsuzaka: Department of General Internal Medicine and Infectious Diseases/Palliative Care Team, Teine Keijinkai Hospital; Yoichi Matsuda: Department of Anesthesiology and Intensive Care Medicine, Osaka University graduate School of Medicine; Naoko Matsumoto: Library of St.Luke's College of Nursing; Yoshihisa Matsumoto: Department of Palliative Medicine and Psycho-oncology, National Cancer Center Hospital East; Saori Miura: Department of Nursing, Keio University Hospital; Satoshi Murakami: Department of Palliative Medicine/Psycho-oncology Division, National

Cancer Center; Hiroaki Murata: Department of Anesthesiology, Nagasaki University School of Medicine; Toshikazu Moriwaki: Department of Gastroenterology, University of Tsukuba; Suzu Yae: Palliative Care Team, Cancer Center, Juntendo University; Keisuke Yamaguchi: Department of Anesthesiology and Pain Clinic, Juntendo University School of Medicine; Takashi Yamaguchi: Department of Palliative Medicine, Tsukuba Medical Center Hospital; Ryo Yamamoto: Department of General Medicine/ Palliative Care Team, Saku Central Hospital; Mayu Yunokawa: Division of Cancer Genomics, National Cancer Center Research Institute; Kinomi Yomiya: Department of Palliative Care, Saitama Cancer Center; Emi Ryuu: Department of Pharmacy/Palliative Care Team, Nagasaki University Hospital; Hiroaki Watanabe: Department of Palliative Medicine, Shizuoka Cancer Center; Mari Watanabe: Regional Medical Liaison Office, Kanagawa Cancer Center; Keiko Iino: Department of Adult Nursing, National college of Nursing; Hirohisa Kato: Department of Drug Information, School of Pharmacy, Showa University ; Shohei Kawagoe: Aozora Clinic; Yoshiyuki Kizawa: Institute of Clinical Medicine, Graduate School Comprehensive Human Sciences, University of Tsukuba; Naohito Shimoyama: Department of Palliative Medicine/Psycho-oncology Division, National Cancer Center East; Masashi Chatani: Department of Radiation, Osaka Rosai Hospital; Satoru Tsuneto: Department of Palliative Medicine, Graduate School of Medicine, Osaka University; Yasuo Nakajima: Department of Radiology, St.Marianna University School of Medicine; Takeo Nakayama: Department of Health Informatics, Kyoto University; Masaru Narabayashi: Department of Palliative Medicine, Saitama Medical University International Medical Center; Taketo Mukaiyama: Department of Cancer Palliative Care, The Cancer Institute Hospital Of Japanese Foundation for Cancer Research; Kazushige Murakawa: Department of Pain Medicine, Hyogo College of Medicine.

JOURNAL OF PALLIATIVE MEDICINE
Volume 16, Number 9, 2013

DOI: 10.1089/jpm.2013.0100

Predictive Factors for Agitation Severity of Hyperactive Delirium in Terminally Ill Cancer Patients in a General Hospital Using Ordered Logistic Regression Analysis

Yuko Kanbayashi, PhD, JSOP,[1,2] Yutaka Hatano, MD,[2,3] Yuzuru Hata, MD,[2,3] Tatsuya Morita, MD,[4] Kenji Fukui, MD, PhD,[3] and Toyoshi Hosokawa, MD, PhD[2,5,6]

Abstract

Background: Despite the fact that many cancer patients worldwide die in general hospitals, there are few reports of the analysis of delirium in terminally ill cancer patients in this setting.
Purpose: This study aimed to identify predictive factors for agitation severity of hyperactive delirium in terminally ill cancer patients in a general hospital.
Methods: Participants were 182 consecutively admitted terminally ill cancer patients who died in a Japanese general hospital between April 2009 and March 2011. Variables present one week before death were extracted from the clinical records for regression analysis of factors potentially related to agitation severity of delirium. The prevalence and agitation severity of delirium were evaluated retrospectively. Multivariate ordered logistic regression analysis was performed to identify predictive factors.
Results: Male sex [odds ratio (OR) = 2.125, 95% confidence interval (CI) = 1.111–4.067; $P = 0.0227$]; total bilirubin (T-bil) [OR = 1.557, CI = 1.082–2.239; $P = 0.017$]; antibiotics [OR = 0.450, CI = 0.219–0.925; $P = 0.0298$]; nonsteroidal antiinflammatory drugs (NSAIDs) [OR = 2.608, CI = 1.374–4.950; $P = 0.0034$]; and hematological malignancy [OR = 3.903, CI = 1.363–11.179; $P = 0.0112$] were found to be statistically significant predictors for agitation severity of hyperactive delirium.
Conclusions: Our study indicates that male sex, T-bil, antibiotic therapy, NSAID therapy, and hematological malignancy are significant predictors for agitation severity of hyperactive delirium in terminally ill cancer patients in a general hospital setting.

Introduction

Delirium is one of the psychiatric symptoms that occurs frequently (25% – 85%) in terminally ill cancer patients just before death.[1–5] Delirium is an acute brain syndrome with consciousness disturbance, psychomotor excitement, cognitive deficits, and psychomotor retardation, as opposed to dementia, in which a chronic organic cause affecting the brain is usually identified or likely.[6] From a behavioral point of view, delirium can be classified as hypoactive; hyperactive (i.e., associated with the hypovigilant or hypervigilant level of consciousness); or mixed.[6] In terminally ill cancer patients, delirium can be induced by several factors, such as metabolic disturbance, organ failure, and drugs;[6–8] and the same factors disturb recovery. Even though it is difficult to treat delirium in this population, pharmacological treatments using antipsychotics and/or sedative drugs may be appropriate for agitated delirium, because the condition may cause severe distress for both patients and family members.[9–11] Therefore, although delirium might be considered by some to be a natural part of the dying process,[9,12] the ability to predict the agitation severity of delirium and prevention of this aspect would represent an advance in clinical management of these patients.

[1]Hospital Pharmacy, [2]Department of Pain Treatment and Palliative Care Unit, University Hospital, [3]Department of Psychiatry, [5]Department of Anesthesiology, Graduate School of Medical Science, [6]Department of Pain Management and Palliative Care Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan.
[4]Department of Palliative and Supportive Care, Palliative Care Team, Seirei Hospice, Seirei Mikatahara General Hospital, Shizuoka, Japan.
Accepted March 26, 2013.

Multiple studies have statistically identified predictive factors for delirium in these patients.[1–5,13] However, despite the fact that many cancer patients worldwide die in general hospitals, to the best of our knowledge there are few reports of the analysis of agitation severity of delirium in terminally ill cancer patients in this setting.[14,15] Therefore, a retrospective study was carried out with the primary aim of identifying predictive factors for agitation severity of hyperactive delirium in terminally ill cancer patients in a general hospital.

Methods

Study term and participants

Consecutively admitted adult cancer patients who died at the University Hospital of Kyoto Prefectural University of Medicine between April 2009 and March 2011 were enrolled in this study. This is a 1065-bed core hospital in the Kyoto prefecture, an acute care hospital with no palliative care unit. The inclusion criterion for this study was death due to cancer at the hospital after a stay of seven days or more, because the aim was to identify predictive factors during the week before death. Exclusion criteria were as follows: (1) patients maintained under medical continuous sedation during the final week of life; (2) patients who died suddenly due to unexpected causes (e.g., fatal arrhythmia, pulmonary embolism); (3) patients with dementia; and (4) patients who experienced delirium for more than one week before death.

Previous reports have indicated that in patients with cancer, delirium occurs with greater frequency during the few days before death;[1–5] therefore, we focused on agitation severity during the final week of life. This study was performed with the approval of the Ethics Review Board of Kyoto Prefectural University of Medicine.

Delirium assessment

The hyperactive delirium diagnoses were made by a psychiatrist with 10 years clinical experience using clinical records from the patients' last week. Mental status descriptions in the records were most often written by the treating physician and/or primary nurse. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnostic criteria were used to define delirium.[16] DSM-IV criteria include acute onset of consciousness disturbance, acute onset of cognition disturbance, and fluctuating symptoms. Referring to a previous study,[17] delirium was coded as "present" if any key terms such as inattention, disorientation, hallucinations, agitation, and inadequate behavior were present and acute onset or acute change of symptoms was present. Because of the retrospective nature of the investigation and the great possibility of underestimation of hypoactive delirium, we defined only hyperactive delirium. The agitation severity of hyperactive delirium was also assessed from the records of the last week by the psychiatrist using the "psychomotor activity" item (Item 9) of the Memorial Delirium Assessment Scale (MDAS) following the previous studies.[13,18,19] The rationale for adopting this end-point was that (1) there is no validated method for assessing severity of agitation retrospectively, (2) several studies showed that MDAS Item 9 was associated with neurobehavioral dimension and severity of agitation,[20–22] and (3) it was assumed that remarkable events related to the patients with hyperactive delirium were usually well described in the medical records as a part of routine practice. Then the agitation severity (response variable) was categorized according to an ad hoc scale referring MDAS as follows: 0, no agitation (no episode of delirium or hypoactive delirium); 1, mild; 2, moderate; and 3, severe. The most severe symptom during the final week was ascertained. To calculate interrater reliability of the assessment of both diagnosis of delirium and severity of agitated delirium, 40 patients' records were randomized and assessed under blinded conditions by another psychiatrist with seven years of clinical experience. A kappa coefficient was calculated.

Extraction of variables

Variables possibly related to agitation severity of delirium were extracted from patients' clinical records for regression analysis. According to previous studies,[1–8] categories were chosen. Palliative care team intervention was defined as that occurring before the final week. Laboratory profiles were obtained from blood tests taken one week before death. Medication use was ascertained from prescriptions written one week before death, and anticancer drugs during the final three weeks. Morphine or fentanyl doses were converted to oral or transdermal daily doses, using the standard conversion ratios.[23]

Statistical analyses

Multivariate ordered logistic regression analysis was used, since scoring for agitation severity of delirium was evaluated by a graded scale, and multiple factors involved in scoring were evaluated simultaneously. Variables were screened by examining for multicollinearity (correlation coefficient $|r| > 0.7$), which occurs when correlations existing among variables results in use of an inappropriate model. A multivariate logistic regression model was constructed using forward stepwise selection among several candidate variables with a variable entry criterion of 0.25 and a variable retention criterion of 0.1 (JMP® version 10; SAS Institute, Cary, NC). All statistical analyses were performed at a two-sided significance level of 0.05. Serum creatinine was categorized as either normal (<1.0 mg/dL) or abnormal (≥ 1.0 mg/dL), and T-bil was categorized as either normal (<1.0 mg/dL), a little high (≥ 1.0 mg/dL, <3.0 mg/dL), or high (≥ 3.0 mg/dL). These criteria were based on a previous study.[24] Hydration volume was categorized as none, peripheral hydration, or total parenteral nutrition. Statistical data were analyzed with JMP® version 10 (SAS Institute, Cary, NC). P value < 0.05 was considered to be statistically significant.

Results

Of 317 adult cancer patients who were consecutively admitted to, and subsequently died at, the University Hospital of Kyoto Prefectural University of Medicine during the study period, 135 patients (42.6 %) were excluded based on the defined exclusion criteria, as follows: 4 died of causes not related to cancer (2 heart failures, 1 cerebral infarction, and 1 postsurgical complication); 43 died less than one week after admission; 45 required medical continuous sedation during the final week; 5 died due to unexpected sudden change (2 brain hemorrhages and 2 unknown causes of death); 3 had

TABLE 1. PATIENT CHARACTERISTICS AND ALL EXTRACTED VARIABLES AND THE RESULTS OF UNIVARIATE ANALYSES (N=182)

	Hyperactive delirium (n=80)	*No hyperactive delirium (n=102)*	*P*	*OR (95% CI)*	*Entered into stepwise model*
Demographic factors					
Sex (male), *n* (%)	55 (69)	53 (52)	0.03	2.0 (1.1–3.5)	Yes
Age	63.7 (12.4)	63.5 (14.3)	0.56	1.1 (0.9–1.1)	
PCT intervention final week, *n* (%)	22 (28)	28 (27)	0.66	0.9 (0.5–1.6)	
Family support, *n* (%)	72 (90)	88 (86)	0.42	1.4 (0.6–3.5)	
Marriage status, *n* (%)	66 (83)	75 (74)	0.16	1.7 (0.8–3.4)	Yes
Medical condition					
Bone metastasis, *n* (%)	24 (30)	29 (28)	0.84	1.1 (0.6–2.0)	
Liver metastasis, *n* (%)	33 (41)	37 (36)	0.66	1.1 (0.6–2.0)	
Meningeal infiltration or brain metastasis, *n* (%)	4 (5)	11 (11)	0.11	0.4 (0.1–1.2)	Yes
Hepatic encephalopathy, *n* (%)	10 (13)	10 (10)	0.50	1.3 (0.6–3.2)	
Laboratory test and physical measurement					
BMI	20.4 (3.7)	20.5 (3.6)	0.62	0.9 (0.9–1.1)	
CRP, mg/dL	7.6 (0.2–30.2)	5.7 (0.1–27.3)	0.03	1.1 (1.1–1.2)	Yes
AST, U/L	72 (8–477)	44 (9–671)	0.55	1.1 (0.9–1.1)	
ALT, U/L	43 (6–382)	31 (8–524)	0.58	1.1 (0.9–1.1)	
Albumin, g/dL	2.6 (0.5)	2.7 (0.6)	0.18	0.7 (0.4–1.2)	Yes
Total protein, mg/dL	5.7 (1.1)	5.6 (3.4)	0.23	1.1 (0.9–1.1)	Yes
T-bil (continuous), mg/dL	1.4 (0.2–32.1)	0.8 (0.3–24.7)	0.16	1.1 (0.9–1.1)	
T-bil (category)	34/20/26	61/19/22	0.03	1.4 (1.1–2.0)	Yes
BUN, mg/dL	24.7 (6.3–105.8)	24.7 (6.2–151.1)	0.65	0.9 (0.9–1.1)	
SCr (continuous), mg/dL	0.71 (0.2–4.7)	0.63 (0.2–7.2)	0.31	0.9 (0.7–1.2)	
SCr (category), *n* (%)	26 (33)	29 (28)	0.89	1.1 (0.6–1.9)	
Serum sodium, mEq/L	134 (5.5)	135 (6.3)	0.87	0.9 (0.9–1.1)	
Serum potassium, mEq/L	4.5 (0.91)	4.4 (0.76)	0.24	1.2 (0.9–1.7)	Yes
Serum calcium, mg/dL	8.8 (2.0)	8.6 (1.0)	0.79	1.1 (0.8–1.4)	
WBC, $\times 10^3$ /μL	9.7 (0.1–62.9)	9.9 (1.2–68.2)	0.87	0.9 (0.9–1.1)	
Lymphocyte, $\times 10^3$ /μL	0.76 (0.09–7.8)	0.88 (0.1–3.2)	0.84	1.1 (0.7–1.5)	
PLT, $\times 10^3$ /μL	134 (7–774)	189 (7–601)	0.15	0.9 (0.9–1.1)	Yes
Hb, g/dL	9.0 (2.2)	9.5 (2.4)	0.07	0.9 (0.8–1.1)	Yes
Concomitant medications					
Anticancer drugs (within two weeks), *n* (%)	15 (19)	14 (14)	0.31	1.5 (0.7–3.1)	
Metoclopramide or domperidone, *n* (%)	6 (8)	10 (10)	0.84	0.9 (0.3–2.5)	
Histamine 1-antihistamines, *n* (%)	4 (5)	8 (8)	0.44	0.6 (0.2–2.1)	
Histamin 2-antihistamines, *n* (%)	30 (38)	38 (37)	0.82	1.1 (0.6–1.9)	
Antibiotics, *n* (%)	25 (31)	44 (43)	0.21	0.7 (0.4–1.2)	Yes
Antiviral, *n* (%)	4 (5)	5 (5)	0.98	0.9 (0.3–3.6)	
Hydration volume (category)	9/53/18	26/56/20	0.07	1.5 (1.0–2.4)	Yes
Antidepressants exclude TCA, *n* (%)	4 (5)	1 (1)	0.25	2.6 (0.5–13.2)	Yes
Antipsychotics (excluding prochlorperazine), *n* (%)	10 (13)	11 (11)	0.87	1.1 (0.5–2.6)	
Benzodiazepines in last 24 hours, *n* (%)	32 (40)	42 (41)	0.91	0.9 (0.6–1.7)	
Anticonvulsants, *n* (%)	4 (5)	3 (3)	0.79	1.2 (0.3–5.1)	
Steroids, *n* (%)	40 (50)	48 (47)	0.89	1.1 (0.6–1.8)	
NSAIDs, *n* (%)	39 (49)	34 (33)	0.02	1.9 (1.1–3.4)	Yes
Opioid, *n* (%)	42 (53)	54 (53)	0.75	0.9 (0.5–1.6)	
Daily dosage of opioid					
morphine, mg (oral morphine equivalents)	120 (20–600)	60 (5–360)	0.37	1.1 (0.9–1.1)	
oral oxycodone, mg	12.5 (2.5–60)	20 (2.5–40)	0.43	1.1 (0.9–1.1)	
fentanyl, μg/h (transdermal fentanyl equivalents)	4.2 (1.05–50.4)	4.2 (2.1–8.4)	0.32	1.1 (0.9–1.1)	

(*continued*)

TABLE 1. (CONTINUED)

	Hyperactive delirium (n=80)	*No hyperactive delirium (n=102)*	*P*	*OR (95% CI)*	*Entered into stepwise model*
Primary sites of malignancy					
Lung, *n* (%)	6 (8)	15 (15)	0.19	0.5 (0.2–1.4)	Yes
Gastric, *n* (%)	8 (10)	11 (11)	0.68	0.8 (0.3–2.1)	
Hematological malignancies, *n* (%)	12 (15)	11 (11)	0.19	1.7 (0.8–3.9)	Yes
Breast, *n* (%)	3 (4)	5 (5)	0.78	0.8 (0.2–3.3)	
Colon, *n* (%)	6 (8)	8 (8)	0.73	0.8 (0.3–2.4)	
Pancreas, *n* (%)	4 (5)	7 (7)	0.58	0.7 (0.2–2.4)	
Esophageal, *n* (%)	5 (6)	7 (7)	0.92	0.9 (0.3–2.9)	
Liver, *n* (%)	11 (14)	11 (11)	0.64	1.2 (0.5–2.9)	
Cholangiocarcinoma, *n* (%)	5 (6)	5 (5)	0.95	0.9 (0.3–3.3)	
Gynecologic, *n* (%)	5 (6)	4 (4)	0.66	1.3 (0.4–4.7)	
Ontological, *n* (%)	5 (6)	8 (8)	0.58	0.7 (0.2–2.3)	
Urological, *n* (%)	7 (9)	4 (4)	0.21	2.0 (0.7–6.3)	Yes

Values are median (range) or mean (SD) when appropriate.

Binary scales were female=0 and male=1 for sex; <1.0 mg/dL=0 and ≥1.0 mg/dL=1 for serum creatinine (2); and absent=0 and present=1 for others.

Ordinal scales were <1.0 mg/dL=0, >1.0 mg/dL but ≤3.0 mg/dL=1, and >3.0 mg/dL=2 for T-bil (2); none=0, peripheral parenteral nutrition=1, and total parenteral nutrition=2 for hydration volume.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body-mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; Hb, hemoglobin; NSAIDs, nonsteroidal antiinflammatory drugs; PCT, palliative care team; PLT, platelet; SCr, serum creatinine; T-bil, total bilirubin; TCA, tricyclic antidepressant; WBC, white blood cell.

dementia; and 35 developed prolonged delirium more than one week before death.

Table 1 shows the clinical characteristics of the 182 patients who were ultimately enrolled in this study, as well as various candidate factors possibly related to agitation severity of delirium in terminally ill cancer patients.

Table 2 presents agitation severity in all patients analyzed. The total prevalence in the study population of hyperactive delirium during the final week of life was 44.0% (*n*=80). There was good reliability between raters for the assessment of hyperactive delirium (A kappa coefficient=0.832; 95%CI=0.565–0.922) and ratings agitation severity of MDAS Item 9 (A kappa coefficient=0.605; 95% CI=0.361–0.85).

This analysis identified five independent predictors: male sex, T-bil, antibiotics, NSAIDs, and hematological malignancy (see Table 3).

Discussion

The multivariate logistic regression analysis used in this study demonstrated that male sex, T-bil, antibiotics, NSAIDs, and hematological malignancy were significant predictors for agitation severity of hyperactive delirium in terminally ill cancer patients.

TABLE 2. CATEGORIZATION OF THE AGITATION SEVERITY IN TERMINALLY ILL CANCER PATIENTS

Response	*n=182*
0	102
1	39
2	35
3	6

The response was categorized according to an ad hoc scale referring MDAS as follows: 0, no agitation (no episode of delirium or hypoactive delirium); 1, mild; 2, moderate; and 3, severe.

Consistent with previous reports, the current analysis showed that the agitation severity of delirium in terminally ill cancer patients tended to increase with elevated T-bil level[4,13] and in males.[13] Previous studies also clarified that T-bil or male sex were risk factors for delirium.[25,26] Clinicians need to be alert to the greater risk of agitation of delirium in terminally ill cancer patients having these characteristics.

Regarding a correlation with antibiotics use, a previous study found that infection is a risk factor for delirium.[26] This result might suggest that fever caused by infection may be an actual predictive factor for agitation severity of delirium, and that minimizing its potential occurrence may be an additional reason to use antipyretics for patients with infection.

Previous studies demonstrated that NSAIDs are a risk factor for delirium in terminally ill cancer patients or those

TABLE 3. RESULTS OF ORDERED LOGISTIC REGRESSION ANALYSIS FOR VARIABLES EXTRACTED BY FORWARD SELECTION

Variable	*P*	*OR*	*CI of OR* *Lower 95%*	*CI of OR* *Upper 95%*
Sex (male)	***0.0227***	***2.125***	***1.111***	***4.067***
Meningeal infiltration or brain metastasis	0.1907	0.421	0.115	1.539
T-Bil (category)	***0.017***	***1.557***	***1.082***	***2.239***
Hb	0.0622	0.873	0.757	1.007
Antibiotics	***0.0298***	***0.450***	***0.219***	***0.925***
Hydration volume	0.1095	1.507	0.912	2.490
NSAIDs	***0.0034***	***2.608***	***1.374***	***4.950***
Hematological malignancies	***0.0112***	***3.903***	***1.363***	***11.179***

Data $p<0.05$ indicated in bold and italic.

CI, confidence interval; Hb, hemoglobin; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio; T-bil, total bilirubin.

with a progressive deterioration of cognitive function.[7,8,27,28] On the other hand, the antiinflammatory effects were effective for the prevention of cognitive impairment even in chronic situations.[29] In the current study, NSAIDs were identified as a predictive factor for agitation severity of delirium in terminally ill cancer patients. The reason might be because NSAIDs are usually used in patients with uncontrollable pain[30] and fever. NSAIDs also might cause a potential accumulation of toxic metabolites due to decreased renal function, or anemia from gastrointestinal tract disturbances. To the best of our knowledge, there are few previous reports identifying hematological malignancy as a predictor of delirium in terminally ill cancer patients.[31] Patients with hematological malignancy are sometimes in an isolated environment in their terminal stage, with the medical intention of avoiding the risk of infection; the environment factors could contribute to severity of agitation. Also, our patients with hematological malignancy were isolated in a private room or observation room (data not shown). Clinicians need to be alert to the greater risk of agitated delirium in patients with hematological malignancy. Caraceni and colleagues reviewed all drugs or toxic effects that affect central nervous system (CNS) cholinergic neurons are candidates for causing delirium.[6] The blood-brain barrier of patients with hematological malignancy might be broken down due to polypharmacy or inflammation with high-dose chemotherapy or radiation, and so on. Thus, medicinal products and endogenous substances such as bilirubin may gain access to the CNS with resultant toxicity.[32]

Other studies have demonstrated that factors such as hypoalbuminemia, hydration status, and medications are commonly associated with delirium in this patient population. However, laboratory profiles were obtained from blood tests taken one week before death in our study, showing that most patients suffered from malnutrition. Therefore, there might be no significant difference between the delirium and the no-delirium group in mean albumin levels one week before death. Although hydration status was not associated with severity of delirium significantly, it showed a high odds ratio. Medication use was ascertained from prescriptions written one week before death; opioids or steroids were already prescribed to more than half the patients (opioids, 52%; steroids, 53%). Thus delirium might not have occurred due to new prescription of these drugs, or the dose of opioids (see Table 1) and steroids (data not shown) were not so high, thus delirium might not have occurred due to these drugs.

Limitations

This study has several limitations. First, the retrospective nature of the investigation may have decreased the reliability of the data collected. The assessment of delirium depends on the descriptions or terms in the chart. The assessment of agitation severity also depends on the chart descriptions. Therefore, there is a possibility of misclassification (especially about assessment of hypoactive delirium) due to no documentation about delirium or agitation. Second, this study was performed at a single institute and involved a relatively small number of patients, so the results should be confirmed in a further multicenter study.

Conclusion

Male sex, hematological malignancy, T-bil, antibiotics, and NSAIDs were shown to be predictors for agitation severity of hyperactive delirium in terminally ill cancer patients in a general hospital setting. These findings should be considered preliminary and in need of further refinement and study.

Author Disclosure Statement

No competing financial interests exist.

References

1. Bruera E, Miller L, McCallion J, Macmillan K, Krefting L, Hanson J: Cognitive failure in patients with terminal cancer: A prospective study. J Pain Symptom Manage 1992;7:192–195.
2. Pereira J, Hanson J, Bruera E: The frequency and clinical course of cognitive impairment in patients with terminal cancer. Cancer 1997;79:835–842.
3. Lawlor PG, Gagnon B, Mancini IL, Pereira JL, Hanson J, Suarez-Almazor ME, Bruera ED: Occurrence, causes, and outcome of delirium in patients with advanced cancer: A prospective study. Arch Intern Med 2000;160:786–794.
4. Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S: Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. J Pain Symptom Manage 2001;22:997–1006.
5. Gagnon P, Allard P, Gagnon B, Mérette C, Tardif F: Delirium prevention in terminal cancer: Assessment of a multicomponent intervention. Psychooncology 2012;21:187–194.
6. Caraceni A, Simonetti F: Palliating delirium in patients with cancer. Lancet Oncol 2009;10:164–172.
7. White C, McCann MA, Jackson N: First do no harm... Terminal restlessness or drug-induced delirium. J Palliat Med 2007;10:345–351.
8. Alagiakrishnan K, Wiens CA: An approach to drug induced delirium in the elderly. Postgrad Med J 2004;80:388–393.
9. Breitbart W, Gibson C, Tremblay A: The delirium experience: Delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 2002;43:183–194.
10. Morita T, Hirai K, Sakaguchi Y, Tsuneto S, Shima Y: Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. Psychosomatics 2004;45:107–113.
11. Morita T, Akechi T, Ikenaga M, Inoue S, Kohara H, Matsubara T, Matsuo N, Namba M, Shinjo T, Tani K, Uchitomi Y: Terminal delirium: Recommendations from bereaved families' experiences. J Pain Symptom Manage 2007;34:579–589.
12. Breitbart W, Chochinov HM, Passik SD: Psychiatric aspects of palliative care. In: Doyle D, Hanks GW, MacDonald N (eds): *Oxford Textbook of Palliative Medicine, 2nd ed.* New York: Oxford University Press, 1998, pp. 216–247.
13. Morita T, Tei Y, Inoue S: Impaired communication capacity and agitated delirium in the final week of terminally ill cancer patients: Prevalence and identification of research focus. J Pain Symptom Manage 2003;26:827–834.
14. Fried TR, van Doorn C, O'Leary JR, Tinetti ME, Drickamer MA. Older persons' preferences for site of terminal care. Ann Intern Med 1999;131:109–112.
15. Cohen J, Houttekier D, Onwuteaka-Philipsen B, Miccinesi G, Addington-Hall J, Kaasa S, Bilsen J, Deliens L: Which patients with cancer die at home? A study of six European countries using death certificate data. J Clin Oncol 2010;28:2267–2273.

16. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* Text revision. DSM IV-TR. Washington, DC: American Psychiatric Press, 2000.
17. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST Jr, Leslie DL, Agostini JV: A chart-based method for identification of delirium: Validation compared with interviewer ratings using the confusion assessment method. J Am Geriatr Soc 2005;53:312–318.
18. Breitbart W, Rosenfeld B, Roth A, Smith MJ, Cohen K, Passik S: The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997;13:128–137.
19. Nagase M, Okamoto Y, Tsuneto S, Tanimukai H, Matsuda Y, Okishiro N, Oono Y, Tsugane M, Takagi T, Uejima E: A retrospective chart review of terminal patients with cancer with agitation and their risk factors. J Palliat Med 2012;15: 1185–1190.
20. Morita T, Tsunoda J, Inoue S, Chihara S, Oka K: Communication Capacity Scale and Agitation Distress Scale to measure the severity of delirium in terminally ill cancer patients: A validation study. Palliat Med 2001;15:197–206.
21. Morita T, Chinone Y, Ikenaga M, Miyoshi M, Nakaho T, Nishitateno K, Sakonji M, Shima Y, Suenaga K, Takigawa C, Kohara H, Tani K, Kawamura Y, Matsubara T, Watanabe A, Yagi Y, Sasaki T, Higuchi A, Kimura H, Abo H, Ozawa T, Kizawa Y, Uchitomi Y; Japan Pain, Palliative Medicine, Rehabilitation, and Psycho-Oncology Study Group: Efficacy and safety of palliative sedation therapy: A multicenter, prospective, observational study conducted on specialized palliative care units in Japan. J Pain Symptom Manage 2005;30:320–328.
22. Lawlor PG, Nekolaichuk C, Gagnon B, Mancini IL, Pereira JL, Bruera ED: Clinical utility, factor analysis, and further validation of the memorial delirium assessment scale in patients with advanced cancer: Assessing delirium in advanced cancer. Cancer 2000;88:2859–2867.
23. Hanks GCW, Cherny N: Opioid analgesic therapy. In: Doyle D, Hanks GCW, MacDonald N (eds): *Oxford Textbook of Palliative Medicine, 2nd ed.* New York: Oxford Medical Publications, 1998, pp. 331–355.
24. Durand F, Valla D: Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol 2005;42:S100–S107.
25. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y: Delirium in an intensive care unit: A study of risk factors. Intensive Care Med 2001;27:1297–1304.
26. Schor JD, Levkoff SE, Lipsitz LA, Reilly CH, Cleary PD, Rowe JW, Evans DA: Risk factors for delirium in hospitalized elderly. JAMA 1992;267:827–831.
27. Macknight C, Rojas-Fernandez CH: Celecoxib- and rofecoxib-induced delirium. J Neuropsychiatry Clin Neurosci 2001;13:305–306.
28. Hoppmann RA, Peden JG, Ober SK: Central nervous system side effects of nonsteroidal anti-inflammatory drugs: Aseptic meningitis, psychosis, and cognitive dysfunction. Arch Intern Med 1991;151:1309–1313.
29. Cunningham C, Skelly DT: Non-steroidal anti-inflammatory drugs and cognitive function: Are prostaglandins at the heart of cognitive impairment in dementia and delirium? J Neuroimmune Pharmacol 2012;7:60–73.
30. Davis MP, Walsh D, Lagman R, LeGrand SB: Controversies in pharmacotherapy of pain management. Lancet Oncol 2005;6:696–704.
31. Fadul NA, El Osta B, Dalal S, Poulter VA, Bruera E: Comparison of symptom burden among patients referred to palliative care with hematologic malignancies versus those with solid tumors. J Palliat Med 2008;11:422–427.
32. Zeevi N, Pachter J, McCullough LD, Wolfson L, Kuchel GA: The blood-brain barrier: Geriatric relevance of a critical brain-body interface. Am Geriatr Soc 2010;58:1749–1757.

Address correspondence to:
Yuko Kanbayashi, PhD, JSOP
Department of Hospital Pharmacy
Kyoto Prefectural University of Medicine
Kawaramachi, Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan

E-mail: ykokanba@koto.kpu-m.ac.jp

Palliative and Supportive Care, page 1 of 6, 2012.

doi:10.1017/S1478951512000569

ORIGINAL ARTICLE

Practices and evaluations of prognostic disclosure for Japanese cancer patients and their families from the family's point of view

SARAN YOSHIDA,[1] MARIKO SHIOZAKI, PH.D.,[2] MAKIKO SANJO, PH.D.,[3] TATSUYA MORITA, M.D.,[4] KEI HIRAI, PH.D.,[5] SATORU TSUNETO, M.D., PH.D.,[6] AND YASUO SHIMA, M.D.[7]

[1]Center for Cancer Control and Information Services, National Cancer Center Tokyo, Japan
[2]International Center for Human Sciences, Kinki University, Higashi-Osaka City, 5, Japan
[3]Department of Adult Health Nursing, Faculty of Medicine, Toho University, Ota-ku, Tokyo, Japan
[4]Department of Palliative and Supportive Care, Palliative Care Team, and Seirei Hospice, Seirei Mikatahara General Hospital, Hamamatsu, Shizuoka 433-8558, Japan
[5]Center for the Study of Communication Design, Graduate School of Human Sciences & Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
[6]Department of Palliative Medicine, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan
[7]Department of Palliative Medicine, Tsukuba Medical Center Hospital, Tsukuba, Ibaraki, Japan

(RECEIVED April 15, 2012; ACCEPTED April 24, 2012)

ABSTRACT

Objective: The primary end points of this analysis were to explore 1) the practices of prognostic disclosure for patients with cancer and their family members in Japan, 2) the person who decided on the degree of prognosis communication, and 3) family evaluations of the type of prognostic disclosure.

Method: Semistructured face-to-face interviews were conducted with 60 bereaved family members of patients with cancer who were admitted to palliative care units in Japan.

Results: Twenty-five percent of patients and 75% of family members were informed of the predicted survival time of the patient. Thirty-eight percent of family members answered that they themselves decided on to what degree to communicate the prognosis to patients and 83% of them chose not to disclose to patients their prognosis or incurability. In the overall evaluation of prognosis communication, 30% of the participants said that they regretted or felt doubtful about the degree of prognostic disclosure to patients, whereas 37% said that they were satisfied with the degree of prognostic disclosure and 5% said that they had made a compromise. Both in the "prognostic disclosure" group and the "no disclosure" group, there were family members who said that they regretted or felt doubtful (27% and 31%, respectively) and family members who said that they were satisfied with the degree of disclosure (27% and 44%, respectively).

Significance of results: In conclusion, family members assume the predominant role as the decision-making source regarding prognosis disclosure to patients, and they often even prevent prognostic disclosure to patients. From the perspective of family members, any one type of disclosure is not necessarily the most acceptable choice. Future surveys should explore the reasons why family members agree or disagree with prognostic disclosures to patients and factors correlated with family evaluations.

KEYWORDS: Prognostic disclosure, Patients, Family, Cancer, Decision making

Address correspondence and reprint requests to: Saran Yoshida, Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan. E-mail: saryoshi@ncc.go.jp

INTRODUCTION

Prognosis is an issue that most physicians and patients describe as difficult to discuss (Hagerty et al., 2005), and whether to tell patients with cancer about their diagnosis and prognosis is a matter of great debate (Harris et al., 2003). Although it is often considered important to give patients prognostic information so that they can make important decisions in an informed manner (Harris et al., 2003), some physicians either avoid the topic (Back et al., 2005; Mack et al., 2006) or disclose vague (The et al., 2000) or overly optimistic information (Lamont & Christakis, 2001).

Whereas many studies have recommend that physicians be the first to disclose the prognosis to the patient (Tang et al., 2006; Hari et al., 2007; Ngo-Metzger et al., 2008) in some cultures, including Japan, physicians are not expected to inform patients that they have a terminal illness (Mystakidou et al., 2004; Yun et al., 2004; Gabbay et al., 2005; Jiang et al., 2007), and family members often receive the information earlier and in more detail than does the patient (Yoshida et al., 2011). In this case, family members can be given decision-making authority and responsibility for the patient even when the patient is competent to make such decisions (Jiang et al., 2007). However, decisions regarding patients' end-of-life concerns generate great distress for family members (Meeker, 2004; Parks & Winter, 2009). For this reason, improving support systems available for family members making difficult end-of-life decisions with regard to prognostic disclosure is an important task for Japanese medical professionals. However, to our knowledge, only a few empirical studies have specifically addressed the practices of prognostic disclosure to patients and family members, including the factor of who makes the decisions. Moreover, family evaluations of the types of prognostic disclosure have not been explored.

The primary end points of this analysis were, therefore, to explore 1) the practices of prognostic disclosure for patients with cancer and their family members in Japan, 2) the person(s) deciding how to communicate the prognosis, and 3) family evaluations of the various types of prognostic disclosure.

METHOD

Procedure

This qualitative study was conducted as the second part of a nationwide questionnaire survey of 8402 bereaved family members of cancer patients who died in certified hospice and palliative care units in Japan. The procedures related to the original survey are described in a previous article (Miyashita et al., 2008).

We conducted semistructured face-to-face interviews between April and August 2008. Each interview was tape recorded. The interviewers included two psychologists, a research nurse, and three graduate students. The interviews followed an interview guideline developed by the authors and was tailored to the purpose of this study. The interview contained predetermined open-ended questions as follows: 1) How were you and the patient told about the patient's prognosis? 2) Who decided on the method of prognosis disclosure? 3) How do you perceive the way prognosis was disclosed to you and the patient?

Participants

For this study, we analyzed 105 family members who met two criteria: agreement to respond to an interview recruitment, and ability to attend face-to-face interviews. Subsequent participation was by mail.

The interviewer explained the purpose and method of the study in detail and obtained written informed consent from all the participants. Ethical and scientific validity were confirmed by the institutional review board of the Graduate School of Human Sciences, Osaka University.

Analysis

All interviews were tape recorded and transcribed. Content analysis was performed on the transcribed data. First, each interviewer identified the type of prognostic disclosure to the patient and participant from the following characteristics: 1) survival periods (e.g. "until May" or "several weeks"), 2) information only about incurability (they did not receive information related to survival periods), 3) no disclosure (they did not receive any disclosure at all), or 4) overly optimistic information (they were told the patient is not incurable). Second, each interviewer also identified the person who decided how to disclose prognosis to the patient and participant from the following categories: 1) patient, 2) family member, 3) physician or nurse, or 4) no discussion. Next, researchers extracted all statements from the transcripts related to familial evaluations of prognostic disclosure. Then, we carefully broke down family evaluations into four categories from 1) satisfied, 2) made a compromise, 3) feelings of doubt, and 4) feelings of regret. Finally, two coders chosen from psychology students independently determined the family evaluation of prognostic disclosure for each participant. When their coding was

Table 1. *Background of patients and the bereaved families*

	n	%
Total	60	
Patients		
Age (mean ± SD)	69 ± 11	
Sex		
Male	39	65.0
Female	21	35.0
Primary tumor sites		
Lung	14	23.3
Colon	8	13.3
Stomach	5	8.3
Breast	4	6.7
Pancreas	3	5.0
Ovary	3	5.0
Others	23	38.3
Bereaved families		
Age (mean ± SD)	59 ± 11	
Sex		
Male	23	38.3
Female	37	61.7
Relationship to the decreased		
Spouse	30	50.0
Child	19	31.7
Child-in-law	3	5.0
Sibling	4	6.7
Other	4	6.7
Mean intervals from patient death (mean ± SD, month)	23 ± 2	

inconsistent, they discussed further and made a final judgment.

RESULTS

Of the 105 family members initially recruited, 60 members participated in the survey (response rate 57.1%). Table 1 summarizes the background information for the patients and participants.

Family-Reported Practices of Prognostic Disclosure

The types of prognosis communication that patients received were divided into the following characteristics: well-defined, predicted survival periods (25.0%, $n = 15$), communication of incurability without well-defined, predicted survival periods (11.7%, $n = 7$), no disclosure about incurability (60.0%, $n = 36$), and communication of curability (3.3%, $n = 2$). Meanwhile, the types of prognostic disclosures that participants received were: well-defined, predicted survival periods (75.0%, $n = 45$), communication of incurability without well-defined, predicted survival periods (23.3%, $n = 14$), and no disclosure about incurability (1.7%, $n = 1$).

Individuals Who Decided on the Type of Prognostic Disclosure

The individuals who decided on the degree of prognostic disclosure to patients broke down into the following groups: patient (8.3%, $n = 5$), family member (38.3%, $n = 23$), physician or nurse (31.7%, $n = 19$), and no one/no discussion (21.7%, $n = 13$). In comparison, the person who decided the degree of prognostic disclosure to family members broke down as follows: family member (15.0%, $n = 9$), physician or nurse (80.0%, $n = 48$), and no one/no discussion (5.0%, $n = 3$). Table 2 shows detailed results regarding the decision makers. A large majority of family members (19 out of 23) who decided on the degree of disclosure by themselves chose not to disclose to patients information related to prognosis and incurability, whereas 15 of 19 cases in which the physician or nurse decided the degree of disclosure chose to disclose prognosis or incurability information to patients.

Family Evaluations of the Type of Prognostic Disclosure

In total, 23 participants (38.3%) told us that they felt satisfied with the degree of prognostic disclosure, 4 participants (6.7%) revealed that they made a compromise related to disclosure, 13 participants (21.7%,) said that they felt doubtful, and 6 participants (10.0%) felt regret. In comparison, 20 participants (33.3%) said that they felt satisfied with the degree of prognostic disclosure for patients, 5 participants (8.3%) said that they felt doubtful, and 5 participants (8.3%) experienced regret. The concordance rate of the determinations of the evaluations by the two coders was 92.6%. Table 3 provides detailed results regarding the family evaluations of prognostic disclosure. The percentage of family members who reported that they were satisfied with the degree of disclosure to patients was 26.7% in the "prognostic disclosure" group, and 44.4% in the "no disclosure" group. The percentage of family members who reported that they either regretted or felt doubtful about the degree of disclosure to patients was 26.6% in the "prognostic disclosure" group, and 30.5% in the "no disclosure" group.

DISCUSSION

In Japan, an important task for medical professionals is to improve the support system for family members regarding prognostic disclosure. Our study is, to our knowledge, the first survey to investigate family evaluations of prognostic disclosure to both patients and family members, including an analysis of who makes such decisions.

Table 2. *Decision maker for the type of prognostic disclosure*

	Total		Prognostic disclosure (survival periods)		Incurability disclosure (only about incurability)		No disclosure (no prognostic information)		Optimistic disclosure (overly optimistic information)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Disclosure for patient	60		15		7		36		2	
Patient	5	8.3	3	20.0	0	0.0	2	5.6	0	0.0
Family member	23	38.3	2	13.3	0	0.0	19	52.8	2	100.0
Physician or nurse	19	31.7	8	53.3	7	100.0	4	11.1	0	0.0
No discussion	13	21.7	2	13.3	0	0.0	11	30.6	0	0.0
Disclosure for family members	60		45		14		1		0	
Patient	0	0.0	0	0.0	0	0.0	0	0.0	0	–
Family member	9	15.0	9	20.0	0	0.0	0	0.0	0	–
Physician or nurse	48	80.0	29	64.4	19	135.7	0	0.0	0	–
No discussion	3	5.0	2	4.4	0	0.0	1	100.0	0	–

Table 3. *Family evaluation on prognostic disclosure*

	Total		Prognostic disclosure (survival periods)		Incurability disclosure (only about incurability)		No disclosure (no prognostic information)		Optimistic disclosure (overly optimistic information)	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Disclosure for patient	60		15		7		36		2	
Feel satisfied	22	36.7	4	26.7	2	28.6	16	44.4	0	0.0
Make a compromise	3	5.0	0	0.0	0	0.0	3	8.3	0	0.0
Feel doubtful	12	20.0	2	13.3	2	28.6	7	19.4	1	50.0
Regret	6	10.0	2	13.3	1	14.3	3	8.3	0	0.0
No evaluation	17	28.3	7	46.7	2	28.6	7	19.4	1	50.0
Disclosure for family members	60		45		14		1		0	
Feel satisfied	20	33.3	17	37.8	3	21.4	0	0.0	0	–
Make a compromise	0	0.0	0	0.0	0	0.0	0	0.0	0	–
Feel doubtful	5	8.3	3	6.7	2	14.3	0	0.0	0	–
Regret	5	8.3	2	4.4	3	21.4	0	0.0	0	–
No evaluation	30	50.0	23	51.1	6	42.9	1	1.7	0	–

Our survey evaluated prognostic disclosure practices in Japan for patients with cancer and their family members. Whereas only 25% of patients were provided predictions of survival periods, >70% of the family members received prognostic disclosures. This agrees with the notion that physicians are not expected to inform patients that they have a terminal illness in Japan and other Asian countries (Tang & Lee, 2004; Gabbay et al., 2005; Yoshida et al., 2011). It can be said that the main targets of prognostic disclosures in Japan are still family members.

The most important finding is that only ~30% of medical professionals assume responsibility for the degree of prognostic disclosure to patients, whereas >80% assume responsibility in case of disclosure to family members. Thirty-seven percent of participants reported that they themselves decided on what degree of prognosis communication was appropriate. These data agree with the notion that family members are sometimes given decision-making authority and responsibility for the patient in Asian countries (Jiang et al., 2007). It is also notable that 18 of 22 participants who decided how to disclose the prognosis to the patient chose not to disclose any information at all. Honest, timely, and complete prognostic disclosure is a key determinant of the overall satisfaction of patients (LeClaire et al., 2005; Heyland et al., 2006), and in Japan, ~50% of patients preferred to receive information about the expected length of survival (Fujimori et al., 2007). The result of this study shows that family members can often prevent patients themselves from receiving adequate prognostic disclosure. Therefore, further investigations should determine precisely why family members either agree or disagree with prognostic disclosures to patients, in order to understand whether the decisions of family members are reasonable, and to possibly support more empathetic communication.

Another important finding from this study was that >30% of family members regretted or felt doubtful about the types of prognostic disclosure to patients, whereas 38% of participants were satisfied with the way prognoses were disclosed. It is notable that there were some family members who were satisfied with prognostic disclosure and some who regretted it in every type of disclosure group. Previous studies showed that prognosis discussions enhance patients' and family members' satisfaction with end-of-life care. (Heyland et al., 2009; Innes & Payne, 2009) However, our results suggest that any one type of disclosure is not necessarily always the most acceptable choice for family members. Therefore it would be important to clarify factors that correlate with the differences in evaluation among family members who made the same decision.

This study had several limitations. First, as the number of participants was small and the response rate was not very high (57.1%), the study subjects might not be representative of the whole population. Second, the study subjects were limited to the families of patients who had been admitted to palliative care units, and the findings might not be applicable to families/patients in other settings. A future survey of families of patients who have not been admitted to palliative care units represents an expected next step in this research. Third, both practices and evaluations were explored from the family members' point of view. Further research including patients' perceptions will be needed. Finally, this study depended upon retrospective evaluations obtained from bereaved family members, and recall bias could exist. Confirmation of our findings will require prospective observational studies.

ACKNOWLEDGMENTS

This study was supported in part by a grant-in-aid for Cancer Research from the Japanese Ministry of Labor, Health and Welfare.

REFERENCES

Back, A.L., Arnold, R.M. Baile, W.F., et al. (2005). Approaching difficult communication tasks in oncology. *CA: A Cancer Journal for Clinicians, 55*, 164–177.

Fujimori, M., Akechi, T. Morita, T. et al. (2007). Preferences of cancer patients regarding the disclosure of bad news. *Psychooncology, 16*, 573–581.

Gabbay, B.B., Matsumura, Etzioni, S., et al. (2005). Negotiating end-of-life decision making: a comparison of Japanese and U.S. residents' approaches. *Academic Medicine, 80*, 617–621.

Hagerty, R.G., Butow, P. N., Ellis, P. M., et al. (2005). Communicating prognosis in cancer care: A systematic review of the literature. *Annals of Oncology, 16*, 1005–1053.

Hari, D., Mark, Z., Bharati, D., et al. (2007). Patients' attitude towards concept of right to know. *Kathmandu University Medical Journal, 5*, 591–595.

Harris, J.J., Shao, J. & Sugarman, J. (2003). Disclosure of cancer diagnosis and prognosis in Northern Tanzania. *Social Science & Medicine, 56*, 905–913.

Heyland, D.K., Allan, D.E., Rocker, G., et al. (2009). Discussing prognosis with patients and their families near the end of life: Impact on satisfaction with end-of-life care. *Open Medicine, 3*, e101–110.

Heyland, D.K., Dodek, P., Rocker, G., et al. (2006). What matters most in end-of-life care: perceptions of seriously ill patients and their family members. *Canadian Medical Association Journal, 174*, 627–633.

Innes, S. & Payne, S. (2009). Advanced cancer patients' prognostic information preferences: a review. *Palliative Medicine, 23*, 29–39.

Jiang, Y., Liu, C., Li, J.Y., et al. (2007). Different attitudes of Chinese patients and their families toward truth telling of different stages of cancer. *Psychooncology, 16*, 928–936.

Lamont, E.B. & Christakis, N.A. (2001). Prognostic disclosure to patients with cancer near the end of life. *Annals of Internal Medicine, 134*, 1096–1105.
LeClaire, M.M., Oakes, J.M., & Weinert, C.R. (2005). Communication of prognostic information for critically ill patients. *Chest, 128*, 1728–1735.
Mack, J.W., Wolfe, J., Grier, H.E., et al. (2006). Communication about prognosis between parents and physicians of children with cancer: Parent preferences and the impact of prognostic information. *Journal of Clinical Oncology, 24*, 5265–5270.
Meeker, M.A. (2004). Family surrogate decision making at the end of life: Seeing them through with care and respect. *Qualitative Health Research, 14*, 204–225.
Miyashita, M., Morita, T., Tsuneto, S., et al. (2008). The Japan Hospice and Palliative Care Evaluation study (J-HOPE study): Study design and characteristics of participating institutions. *The American Journal of Hospice & Palliative Care, 25*, 223–232.
Mystakidou, K., Parpa, E. Tsilila, E., et al. (2004). Cancer information disclosure in different cultural contexts. *Supportive Care in Cancer, 12*, 147–154.
Ngo-Metzger, Q., August, K. J. Srinivasan, M., et al. (2008). End-of-Life care: guidelines for patient-centered communication. *American Family Physician, 77*, 167–174.
Parks, S.M. & Winter, L. (2009). End of life decision-making for cancer patients. *Primary Care, 36*, 811–823.
Tang, S.T. & Lee, S. Y. (2004). Cancer diagnosis and prognosis in Taiwan: Patient preferences versus experiences. *Psychooncology, 13*, 1–13.
Tang, S.T., Liu, T. W. Lai, M. S., et al. (2006). Congruence of knowledge, experiences, and preferences for disclosure of diagnosis and prognosis between terminally-ill cancer patients and their family caregivers in Taiwan. *Cancer Investigation, 24*, 360–366.
The, A.M., Hak, T., Koeter, G., et al. (2000). Collusion in doctor–patient communication about imminent death: an ethnographic study. *BMJ (Clinical Research ed.), 321*, 1376–1381.
Yoshida, S., Hirai, K., Morita, T., et al. (2011). Experience of Families of Japanese Patients with Cancer for Prognostic Disclosure. *Journal of Pain and Symptom Management, 41*, 594–603.
Yun, Y.H., Lee, C. G., Kim, S. Y., et al. (2004). The attitudes of cancer patients and their families toward the disclosure of terminal illness. *Journal of Clinical Oncology, 22*, 307–314.

Support Care Cancer (2013) 21:2777–2781
DOI 10.1007/s00520-013-1846-z

ORIGINAL ARTICLE

Sublingually administered scopolamine for nausea in terminally ill cancer patients

Kengo Imai · Masayuki Ikenaga · Tomoyuki Kodama · Seitetsu Kanemura · Keiko Tamura · Tatsuya Morita

Received: 26 January 2013 / Accepted: 7 May 2013 / Published online: 31 May 2013

Abstract
Purpose The primary aim of this study was to clarify the effect of sublingual scopolamine on the intensity of nausea.
Patients and methods This was an open uncontrolled study, and the study participants were cancer patients consecutively admitted to a palliative care unit in Japan. When the patients had nausea, they were administered a solution of scopolamine at 0.15 mg sublingually. The intensities of nausea were assessed using the 6-point Numerical Rating Scale (NRS 0 = no nausea to 5 = worst nausea) before and 15, 30, and 60 min after administration. Primary endpoints were (1) changes in the NRS of nausea and (2) percentage of patients who achieved a decrease in NRS of 1 or more points 15 min after treatment.
Results Twenty-six patients were recruited for this study. The median NRS significantly decreased from 3.0 (range, 1–5) to 1.5 (0–5) after 15 min, and 84 % (n=21) of the patients achieved a decrease in NRS of 1 or more points after 15 min. In addition, the median NRS significantly decreased from 3.0 (before) to 0 (30 min) and 0 (60 min). The percentage of patients who achieved a decrease in NRS over 1 point was 96 % (n=25) in 30 min and 100 % (n=26) in 60 min. Fifteen percent (n=4) showed drowsiness. No other adverse effects were reported.
Conclusion Sublingually administered scopolamine may be effective for managing nausea in terminally ill cancer patients. Randomized controlled trials are promising.

Keywords Scopolamine · Nausea · Sublingual · Cancer patients · Numerical Rating Scale

K. Imai (✉)
Seirei Hospice, Seirei Mikatahara General Hospital, 3453 Mikatahara-Cho, Kita-Ku,
Hamamatsu, Shizuoka 433-8558, Japan
e-mail: k.imai@sis.seirei.or.jp

M. Ikenaga
Yodogawa Christian Hospital, Hospice Children's Hospice Hospital, 1-7-50, Kunijima, Higashi Yodogawa-Ku,
Osaka 533-0024, Japan

T. Kodama
Kodama Home Care Clinic, 2-7-1-1-101, Tsukuho,
Tsukuba, Ibaraki 300-3257, Japan

S. Kanemura
Department of Palliative Medicine, Takatsuki Red Cross Hospital, 1-1-1, Abuno,
Takatsuki, Osaka 569-1045, Japan

K. Tamura
Nursing Department, Yodogawa Christian Hospital, 1-7-50, Kunijima, Higashi Yodogawa-Ku,
Osaka 533-0024, Japan

T. Morita
Department of Palliative and Supportive Care, Palliative Care Team, and Seirei Hospice, Seirei Mikatahara General Hospital, 3453 Mikatahara-Cho, Kita-Ku,
Hamamatsu, Shizuoka 433-8558, Japan

Introduction

Nausea and vomiting are distressing experiences for patients with advanced cancer. Approximately 60 % of patients with advanced cancer report nausea and 30 % report vomiting [1]. Its presence causes marked physical and psychosocial distress for both patients and their families.

There are two main approaches to drug selection for nausea. One is an etiology-based approach, where antiemetic selection is based on the current understanding of the neuropharmacology of the emetic pathway [2]. Previous studies revealed that an etiology-based approach is effective in more than 80 % of patients with nausea and vomiting [3, 4]. These studies, however, did not assess the effectiveness of each single antiemetic. The other is an empirical approach, using a single antiemetic irrespective of the underlying cause of nausea, and several studies have suggested that this approach