Psycho-Oncology
Psycho-Oncology **21**: 187–194 (2012)
Published online 19 December 2010 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.1881

Delirium prevention in terminal cancer: assessment of a multicomponent intervention

Pierre Gagnon[1,2,3,4,5,6]*, Pierre Allard[7], Bruno Gagnon[8], Chantal Mérette[6] and François Tardif[1,5]

[1]*Centre de Recherche en Cancérologie, l'Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec, Quebec City, QC, Canada*
[2]*Department of Psychiatry, l'Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec, Quebec City, QC, Canada*
[3]*Faculty of Pharmacy, Laval University, Quebec City, QC, Canada*
[4]*Department of Psychiatry, Laval University, Quebec City, QC, Canada*
[5]*Maison Michel Sarrazin, Quebec City, QC, Canada*
[6]*Centre de Recherche Université Laval Robert-Giffard, Quebec City, QC, Canada*
[7]*Division of Palliative Care, Department of Medicine, University of Ottawa, Ottawa, ON, Canada*
[8]*Department of Medicine, Faculty of Medicine, McGill University, Montréal, QC, Canada*

** Correspondence to: Hôtel-Dieu de Québec, Centre Hospitalier Universitaire de Québec, 11 Côte du Palais, Québec, QC, Canada, G1R 2J6. E-mail: pierre.gagnon@crhdq.ulaval.ca*

Received: 11 June 2010
Revised: 14 October 2010
Accepted: 15 October 2010

Abstract

***Objective*: Delirium is a highly prevalent and deleterious disorder in terminally ill cancer patients. We assessed whether a multicomponent preventive intervention was effective in decreasing delirium incidence and severity among cancer patients receiving end-of-life care.**

***Methods*: A cohort of 1516 patients was followed from admission to death at seven Canadian palliative care centers. In two of these centers, routine care included a delirium preventive intervention targeting physicians (written notice on selective delirium risk factors and inquest on intended medication changes), patients, and their family (orientation to time and place, information about early delirium symptoms). Delirium frequency and severity were compared between patients at the intervention ($N = 674$) and usual-care ($N = 842$) centers based on thrice-daily symptom assessments with the Confusion Rating Scale.**

***Results*: The overall rate of adherence to the intervention was 89.7%. The incidence of delirium was 49.1% in the intervention group, compared with 43.9% in the usual-care group (odds ratio [OR] 1.23, $P = 0.045$). When confounding variables were controlled for, no difference was observed between the intervention and the usual-care groups in delirium incidence (OR 0.94, $P = 0.66$), delirium severity (1.83 vs 1.92; $P = 0.07$), total days in delirium (4.57 vs 3.57 days; $P = 0.63$), or duration of first delirium episode (2.9 vs 2.1 days; $P = 0.96$). Delirium-free survival was similar in the two groups.**

***Conclusion*: A simple multicomponent preventive intervention was ineffective in reducing delirium incidence or severity among cancer patients receiving end-of-life care. Delirium prevention remains a difficult challenge in terminally ill cancer patients.**
Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: delirium; terminal cancer; multicomponent intervention; monitoring; palliative care; oncology

Introduction

Delirium is a highly prevalent and deleterious complication in patients with terminal cancer, affecting around 50% of patients [1–6]. It results in an acute confusional state. Pain and symptom management becomes very difficult since clinical assessment is blurred by the patient's confusion, agitation, and loss of ability to communicate adequately [3,7]. Delirium generates a high degree of distress among patients, family, and staff [8]. Urgent and intensive psychosocial intervention is usually required to provide family members with supportive counseling on proper ways to deal with delirium symptoms [9]. If efficacious, prevention would be the best option to avoid the suffering caused by delirium.

In those with terminal cancer, delirium is induced by numerous factors such as brain or meningeal involvement from metastatic lesions, high opioid intake [10–14], metabolic disturbances, and vital organ failure [15]. These risk factors are different from those identified in geriatric populations, such as vision or hearing impairment. The feasibility of primary delirium prevention in patients with terminal cancer has not been established. Preliminary evidence from a study conducted in terminally ill cancer suggested that prompt delirium recognition may lead to more effective clinical management [7,16]. Delirium

Copyright © 2010 John Wiley & Sons, Ltd.

improvement occurred more often in newly developed incident cases than in prevalent cases at time of admission. Thus, there is evidence to suggest that close clinical monitoring and early detection may decrease the severity of delirium [17–20].

A study conducted in geriatric settings by Inouye *et al.* [21] demonstrated the efficacy of a multicomponent intervention in decreasing by 34% the incidence of delirium among patients hospitalized for diverse medical complications. We conducted a controlled clinical trial to evaluate whether a minimal multicomponent preventive intervention would be effective in reducing the incidence of delirium among cancer patients admitted to a palliative care center for end-of-life care.

Methods

Study design

We conducted a nonrandomized clinical trial to determine whether the incidence of delirium would be lower in two palliative care centers where a multicomponent preventive intervention was implemented when compared with baseline delirium incidence in five other usual-care palliative care centers. A randomized delirium prevention trial comparing intervention and usual care within the same unit was not possible because the preventive intervention had to be fully integrated into routine clinical care, and 'contamination' of the intervention on patients receiving usual care would have unavoidably occurred.

Study settings and population

The delirium preventive intervention was implemented in the two centers of the principal investigators to facilitate logistic aspects: Maison Michel-Sarrazin, a 15-bed stand-alone hospice in Quebec City, and the 36-bed Palliative Care Unit at the Élisabeth Bruyère Hospital, in Ottawa, Canada. The five other palliative care centers were located in Montreal, either as dedicated hospital units (Montreal General Hospital, Royal Victoria Hospital, and Mount Sinai Hospital) or in stand-alone hospices (Maison Victor Gadbois and West Island Hospice). The study was approved by each institution's ethics review board. Information about the ongoing study was provided to patients and family members. Patients' written consent was waived since the study procedures and the delirium preventive intervention were part of the daily routine care.

Study exclusion criteria included: (1) patient delirious at admission; (2) patient delirious within 48 h after admission; (3) patient hospitalized <48 h and more than 90 days; and (4) patient still alive at discharge.

Study procedures

A research staff nurse oversaw study procedures in every participating center. Bedside nurses attended a training session on how to screen for and monitor delirium symptoms using the Confusion Rating Scale (CRS) [22–24], an observation-based scoring tool. At the end of each 8-h work shift, the bedside nurse assessed the presence and intensity of disorientation, inappropriate behavior, inappropriate communication, and illusions or hallucinations using a score of 0 (no symptom), 1 (symptom sometimes present, but mild), or 2 (symptom severe in frequency and/or in intensity). CRS completion usually required <2 min. If a score could not be assigned, the reason was recorded (natural sleep, induced sedation, or coma throughout the entire 8-h period). A cutoff score of 2 was associated with a better sensitivity of the CRS screening [7]. In the original CRS validation study, patients having CRS scores of 1 did not have significant alteration of mental status according to the Short Portable Mental Status Questionnaire [23]. Physicians, nurses, and research assistant were not blinded to CRS scores.

According to the original study protocol, any patient with a CRS score of 2 or higher was scheduled to undergo a delirium diagnostic assessment within 24 h using the Confusion Assessment Method (CAM). However, the CAM was obtained in only 39% of candidate patients for logistic reasons related to the challenge of conducting the baseline CAM structured interview in the last days or hours of life. In addition, delays to conduct the CAM rendered the results invalid; hence, it could not be used as an outcome variable or as a valid indicator of CRS sensitivity.

Delirium preventive intervention

The delirium preventive intervention included a patient/physician component and a family component.

Patient/physician component

At the time of admission, the research nurse filled a special form about the patient's status concerning the following delirium risk factors: (1) Eastern Cooperative Oncology Group (ECOG) performance status [25], (2) brain/meninges metastases, (3) known metabolic disturbances, (4) opioid analgesic medication dosage >80 mg of parenteral morphine equivalent per day, (5) benzodiazepine medication dosage of 2 mg or more of lorazepam equivalent per day, and (6) intake of anticholinergics, corticosteroids, or anticonvulsants [26–29]. The delirium risk assessment form was transmitted to the physician and kept in the medical record. The form included a query to the physician about planned medication change to minimize subsequent delirium risk. The bedside nurse was also

Copyright © 2010 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

instructed to orient the patient daily as early as possible in the work shift, by introducing herself and informing the patient of the day of the week, the date, the time, and the place.

Family component

As soon as possible following admission, the bedside nurse provided baseline education to the closest family member about delirium and its symptoms, according to a procedure developed by our group [16]. In addition, the bedside nurse provided the relative with the American College of Physicians recommendations for avoiding symptoms of confusion in patients with advanced cancer [30].

Data collection and analysis

Study data were collected systematically each day by the research nurse. Dosages of opioids, benzodiazepines, and antipsychotics, both administered regularly and on an as-needed basis, were recorded daily. Demographic data and psychiatric diagnoses were retrieved from the medical chart. In these palliative care units and end-of-life situations, no specific co-interventions are performed. Consultations by psychiatrists occur in a small minority of patients and were not recorded systematically. All collected data were independently entered twice to avoid potential errors. Statistics were performed by an experienced biostatistician (CM).

To assess the level of adherence to study procedures, we computed CRS completion rates per group and compared them using the Wilcoxon rank-sum test. An overall estimate of completion rate was also obtained by summing the number of nurse shifts during which a CRS score was assigned and dividing it by the total number of nurse shifts. Rates of adherence to the orientation protocol, the family protocol, the delirium risk level assessment, and the pharmacological recommendations were also determined.

The first step of analysis was to create the following variables based on the CRS scores:

- *First episode of incident delirium* (*yes*/*no*): A patient who had an initial 48-h period of CRS scores = 0 was considered an incident case of delirium if s/he subsequently received at least one CRS score of 2 or higher.
- *Delirium severity score*: Delirium severity score was measured as the mean CRS score throughout the duration of the delirium episode.
- *Duration of first delirium episode*: Delirium duration was estimated by calculating the number of days between the first episode of incident delirium and the resolution of the delirium episode or death.
- *Delirium episode resolution*: A delirium episode was considered resolved if the mean CRS score during six consecutive 8-h work shifts was 0.33 or less following an episode of incident delirium.
- *Proportion of patient-days with delirium symptoms*: This proportion was estimated by computing the number of patient-days on which the CRS score was 2 or higher.

The second step of analysis consisted of tabulating the age, sex, and clinical characteristics (length of hospital stay, ECOG performance status, history of delirium, psychiatric disorder, primary tumor site, and presence of brain metastasis) of patients on admission in order to compare the intervention and usual-care groups using the chi-square test (or Fisher's exact test) for categorical responses and the Wilcoxon rank-sum test for continuous responses.

The characteristics found to distinguish the groups at baseline ($P<0.05$) were identified as potentially confounding variables.

In the third step of analysis, univariate logistic regression was performed to compare crude delirium incidence rates in the two groups. We estimated delirium incidence rates by dividing the number of patients free of delirium symptoms at study onset who subsequently received CRS scores of 2 of higher by the number of patient-days under observation from admission until a first CRS score of 2 or higher, or the end of follow-up. Sensitivity analysis with respect to the choice of the CRS score threshold was conducted. As these analyses produced similar results, only the analysis based on the CRS score threshold of 2 of higher is presented. We also performed multiple logistic regression analyses for categorical outcomes and analysis of covariance on ranks for continuous outcomes while adding length of stay, ECOG status, and past history of delirium as potential confounders.

To compare time to delirium occurrence in the two groups, we performed a survival analysis in which time to delirium was treated as the event while controlling for mean parenteral morphine-equivalent, mean lorazepam-equivalent, and mean antipsychotic daily dosage, based on standard equivalent conversion tables for these drugs [31–34].

All statistical analyses were performed under the supervision of Chantal Mérette, with SAS statistical software (version 9.1.3), and all statistical tests were two-sided. A P-value <0.05 was considered to indicate statistical significance.

Results

Of the 2515 patients with terminal cancer admitted to the seven centers for terminal cancer care during the 3-year period of the study, 507 (20.2%) were

Copyright © 2010 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

delirious on admission or became delirious within the first 48 h. Of the remaining 2008 eligible patients, we excluded from analysis 177 who died within 48 h of admission, 222 who were still alive at discharge, 62 whose hospital stay was longer than 90 days and thus were considered not terminally ill to eliminate outlier data, and 31 who had key missing data. Thus, the study population included 1516 patients, of whom 674 (44.5%) were in the intervention group (Figure 1).

The intervention and usual-care groups differed on several characteristics (Table 1). Compared with the usual-care group, the intervention group was younger (67.6 vs 69.1 years) and had a greater proportion of women, a longer average length of stay (22.2 vs 19.9 days), a better ECOG performance status, and a higher frequency of past delirium (17.3 vs 12.1%). On the other hand, the patients excluded from the study showed a higher frequency of delirium than the included patients (42.0 vs 22.9%). This can be explained by the high proportion of prevalent case in the excluded group (63.5 vs 46.2%).

Level of adherence

A CRS score was assigned in 91.2% of the total 97 680 nursing shifts. The CRS completion rate was higher in the intervention centers than in the usual-care centers (96.6 vs 86.2%), but it did not reach statistical significance and the missing data were taken into account in the analyses. The overall rate of adherence to study protocols was 89.7%. The orientation protocol was done in 84.5% of 13 696 patient-days. Of the 674 patients in the intervention group, 84.1% received the family intervention and the pharmacological risk alert was completed in 91.2%. The most common reasons for noncompliance with study protocols were pharmacological sedation and coma. The main reason for missed family intervention was the absence of a relative. Only global assessments of the dosage of psychoactive medications could be monitored and there were no difference noted between the two groups. More precise changes could not be analyzed since these changes often occur many times over a few days and even during the same day.

Effectiveness of intervention

The crude delirium incidence rate was slightly higher in the intervention group (49.1%) than in the usual-care group (43.9%) (odds ratio [OR] 1.23), but the difference disappeared when potential confounders including length of stay, ECOG status, and past history of delirium were controlled for (OR 0.94) (Table 2). The two groups did not differ with respect to delirium severity score (1.83 vs 1.92), duration of the first delirium episode (2.89 vs 2.1 days), total number of days in delirium (4.57 vs 3.57 days), or proportion of work shifts with a CRS score of 2 or greater. Delirium-free survival time did not differ between the two groups ($P = 0.822$) (Figure 2).

Discussion

Compared with usual care, this multicomponent delirium preventive intervention did not reduce delirium incidence, severity, or duration and did

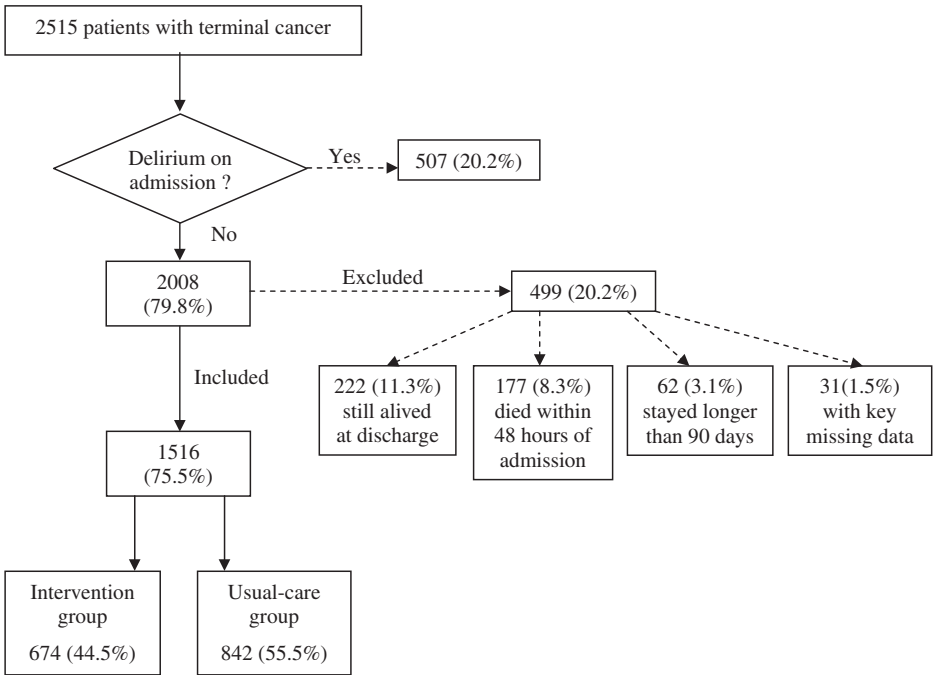

Figure 1. Flow-chart of the included/excluded patients

Copyright © 2010 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

Table 1. Characteristics of the patients on admission

Characteristic	Intervention group (*N* = 674)	Usual-care group (*N* = 842)	*P*-value
Mean age ± SD (years)	67.6 ± 13	69.1 ± 12.9	0.002
No. (and %) female	385 (57)	430 (51)	0.026[a]
Mean hospital stay ± SD (days)	22.2 ± 19	19.9 ± 18.2	0.002[b]
Eastern Cooperative Oncology Group performance status, no. (and %) of patients			<0.001[c]
0—Normal activity level	1 (0.2)	3 (0.4)	
1—Slightly restricted activity level	4 (0.06)	6 (0.8)	
2—Up and about more than 50% of waking hours	73 (10.9)	53 (6.6)	
3—Confined to bed more than 50% of time	298 (44.4)	263 (32.8)	
4—Bedridden	295 (44.0)	477 (59.5)	
History of delirium, no. (and %) of patients			0.034[c]
Yes	114 (17.3)	99 (12.1)	
No	353 (53.4)	426 (52.1)	
Unknown	194 (29.3)	292 (35.8)	
Concomitant condition, no. (and %) of patients			
Depressive disorders	46 (7.0)	20 (2.0)	<0.001[c]
Bipolar disorders	6 (0.9)	2 (0.2)	0.150[a]
Alzheimer's disease	3 (0.5)	3 (0.4)	1.000[a]
Other types of dementia	6 (0.9)	6 (0.7)	0.698[c]
Anxiety disorders	13 (2.0)	5 (0.6)	0.017[c]
Schizophrenia or psychosis	7 (1.0)	2 (0.2)	0.087[a]
Alcoholism	6 (0.9)	0 (0.0)	0.008[a]
Drug dependence	0 (0.0)	1 (0.1)	1.000[a]
Personality disorders	1 (0.2)	1 (0.1)	1.000[a]
Other psychiatric disorders	6 (0.9)	4 (0.5)	0.354[a]
Primary tumor site, no. (and %) of patients			
Respiratory tract (trachea, bronchus, lungs)	166 (24.8)	206 (24.9)	0.941[c]
Digestive system and pleural	110 (16.4)	156 (18.8)	0.262[c]
Colorectal	103 (15.4)	108 (13.0)	0.170[c]
Gynecological	51 (7.6)	56 (6.8)	0.489[c]
Urogenital	31 (4.6)	56 (6.8)	0.088[c]
Breast	65 (9.7)	81 (9.8)	0.988[c]
Prostate	25 (3.7)	30 (3.6)	0.880[c]
Lips, oral cavity, and pharynx	23 (3.4)	17 (2.1)	0.093[c]
Other respiratory tract and thoracic organ	13 (1.9)	9 (1.1)	0.164[c]
Bone, skin, and connective tissue	17 (2.5)	25 (3.0)	0.598[c]
Lymphatic tissue and hematopoietic	22 (3.3)	24 (2.9)	0.641[c]
Glioblastoma and brain	21 (3.1)	24 (2.9)	0.762[c]
Other	23 (3.4)	36 (4.4)	0.388[c]
Brain metastasis	108 (16.0)	126 (15.0)	0.570[c]

SD, standard deviation.
[a]Fisher's exact test.
[b]Wilcoxon rank-sum test.
[c]Chi-square test.
Note: 43 ECOG scores ($n = 1463$), 38 history of delirium ($n = 1466$), and 18 primary tumor site ($n = 1498$) were missing.

not extend delirium-free survival time among inpatients receiving terminal cancer care.

A Cochrane review on delirium prevention concluded that a proactive geriatric consultation was the most promising intervention and that prophylactic haloperidol may be effective to prevent postsurgical delirium [35].

The lack of efficacy in the present trial contrasts with the reported decrease in delirium incidence of 34% following the implementation of a similar multicomponent intervention among geriatric patients admitted for diverse medical complications [21]. The lack of preventive efficacy found in our study may relate to diverse factors pertaining to the intervention, the patients, and the study design. The multicomponent intervention we used in our study was designed for easy implementation and maintenance in the routine care of busy palliative care centers. The psychoeducational family component was kept brief to avoid additional burden on family members. The patient component was designed to minimize the tasks that the bedside nurses would have to carry out. The intervention targeting physicians was nonprescriptive and focused on the provision of baseline information on presumed strong delirium risk factors. It was minimal and more of an educational tone; a more intensive intervention might have been more effective, but implementation and maintenance would have represented a major challenge. In fact,

Copyright © 2010 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

Table 2. Delirium-related outcomes and incidence as defined by a Confusion Rating Scale score of 2 or higher

Outcomes	Intervention group (*N* = 674)	Usual-care group (*N* = 842)	*P*-value	*P*-value when confounding variables controlled for
No. (and %) of patients with first episode of delirium	331 (49.1)	370 (43.9)	0.045[a] (OR = 1.23)	0.660[b] (OR = 0.94)
Mean severity score (mean CRS score) ± SD	1.83 ± 0.71	1.92 ± 0.76	0.082[c]	0.068[d]
Mean duration of first delirium episode ± SD (days)	2.89 ± 5.06	2.10 ± 2.69	0.386[c]	0.962[d]
Mean total no. of days in delirium ± SD	4.7 ± 6.84	3.57 ± 4.75	0.203[c]	0.634[d]
No. (and %) of patients with no CRS score > 0 during hospital stay	172 (25.5)	276 (32.8)	0.002[a] (OR 0.70)	0.490[b] (OR 0.90)
Mean % of nurses' shifts with CRS score ⩾ 2 ± SD	0.056 ± 0.11	0.071 ± 0.14	0.890[c]	0.067[d]

OR, odds ratio.
[a]A univariate logistic regression analysis was performed.
[b]A multiple logistic regression analysis with confounding variables as covariates was performed.
[c]A Wilcoxon rank-sum test was performed.
[d]An analysis of covariance on ranks with confounding variables as covariates was performed.

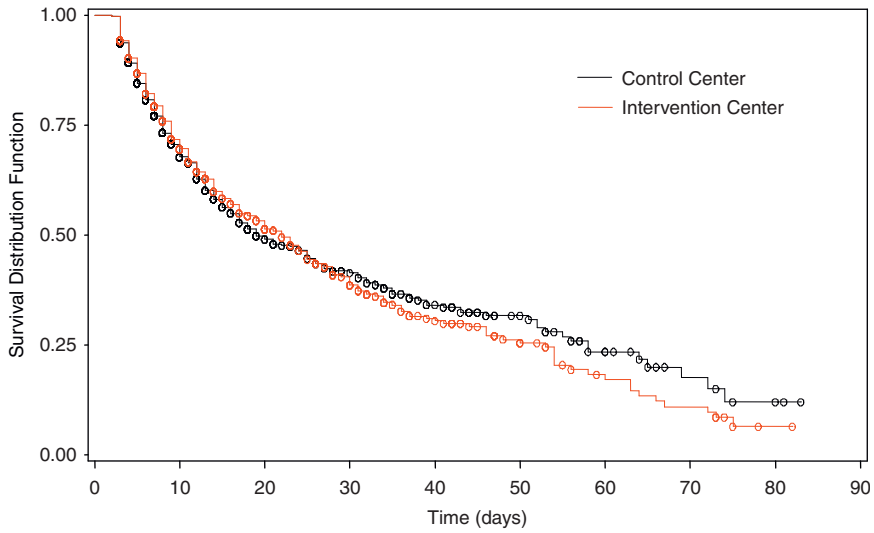

Figure 2. Delirium-free survival of patients in the intervention group vs the usual-care (control) group. Kaplan–Meier survival analysis was used ($P = 0.822$)

it was not possible to implement systematic formal delirium diagnosis using an additional interview, the CAM, over the period of the study. Finally, the characteristics of patients who are dying from metastatic or far advanced cancer represent a challenge for preventive interventions. These patients, who experience cancer progression and have numerous comorbid conditions, are usually treated with complex medication regimens for symptom management. Consequently, they are at high risk for generalized brain dysfunction leading to delirium.

Treating terminally ill patients greatly differs from treating geriatric or surgical patients. In end of life care, delirium precipitating factors such as metabolic dysfunction or brain tumors often cannot be identified or corrected. In addition, past history of delirium may indicate a possible genetic or individual vulnerability that cannot be impacted upon [36,37]. Our study design was prone to contamination bias. To monitor delirium symptoms, we implemented the CRS in both the usual-care and the intervention centers. Thus, nurses and physicians were in a clinical environment where screening for delirium symptoms was part of the routine daily patient monitoring. In fact, implementation of routine monitoring of delirium symptoms is in itself an intervention that might have rendered clinicians more aware of their patients' cognitive status. Their improved awareness may have modified their practice pattern in a way that may reduce the likelihood of delirium. If present, this contamination bias would have reduced our ability to detect a difference in the

Copyright © 2010 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

delirium incidence rate between the two study groups. Although we cannot determine whether and to what extent this bias may have been present, the delirium incidence rate measured in our study is much lower than rates reported in other studies [22], but is in keeping with our previous study [7]. In addition, the study was based on the analysis of incidence of the first delirium episode and not on the cumulative incidence over the entire stay.

Another limitation of our study pertains to the failure to obtain a systematic formal delirium diagnosis in patients who experienced delirium symptoms. The original study protocol included a formal delirium diagnosis using the CAM when a CRS score of 2 or higher was obtained for a first time. However, the CAM diagnostic interview was performed in only 39% of such patients, usually owing to patients' inadequate state of consciousness or fear of excessive patient burden from the diagnostic interview. Delirium misclassification may have occurred based on false-positive or false-negative CRS results, especially pertaining to hypoactive delirium which might have been missed by the CRS. However, sensitivity analyses based on CRS thresholds did not modify the conclusion of the absence of a difference in delirium incidence or severity between the study groups, supporting the validity of the CRS as a reliable indicator of delirium symptoms and an adequate proxy for delirium diagnosis, and arguing against a large misclassification bias.

Our study provides interesting information on the epidemiology of delirium in a large cohort of terminally ill cancer patients. Past history of a delirium episode was the strongest risk factor for the development of delirium, and one-third of patients did not experience any symptom of delirium prior to their death from advanced cancer. These data contrast with some of the literature where higher rates of delirium are reported. It remains a debate whether any important disturbance of state of consciousness in the end of life should be considered a delirium. In this study, the bedside nurses did not rate stupor or pharmacological sedation as delirium, which might explain some of the discrepancy.

Delirium is a major complication of terminal cancer care affecting almost 50% of patients. This multicomponent intervention designed for easy integration into the routine care of palliative centers clearly demonstrated the feasibility of systematic routine daily monitoring of delirium symptoms by bedside nurses. However, improving delirium awareness in families and staff of risk factors is not sufficient to reduce delirium incidence and duration. Nevertheless, results might have been different in another population of patients. Thus, we might start to narrow down on the interventions susceptible to prevent delirium in different settings. Additional studies are needed to evaluate whether prescriptive pharmacological interventions would result in better delirium prevention and outcomes (severity, duration, or quality of life), especially in patients identified at a higher risk such as those with a past history of delirium. It could also be interesting to study to observe if there is a difference in the gender-specific cancer in a younger population. Further research is needed to identify more effective preventive management strategies adapted to palliative care settings.

Acknowledgements

We thank the research coordinator, Line Croteau, and all research nurses: Colette Soulard, R.N., Maison Michel-Sarrazin; Wilma Falconer, R.N., Suzanne Lépine, Montreal General Hospital; Marie-Lucie Bourgon, Liliane Charon, R.N., Élisabeth Bruyère Hospital; Nathalie Savard, Maison Victor-Gadbois; Rose de Angelis, West Island Hospice; and Belle McLean, R.N., Mount Sinai Hospital. We thank Claudia Émond, M.Sc., and Valérie Jomphe, M.Sc., for statistical analysis, Joanie Le Moignan, M.Sc., for revision, and Gloria Baker for editorial assistance. We also thank the nurses, physicians and clinical staff of all the participating units. This research was funded by the National Cancer Institute of Canada (Grant 01-1111, renewal 14371), with funds from the Canadian Cancer Society. At the time of the study, Dr Pierre Gagnon was supported by a Research Scientist award from the Canadian Cancer Society.

References

1. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. *Cancer* 1997;**79**(4):835–842.
2. Lawlor PG, Gagnon B, Mancini IL *et al.* Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Arch Intern Med* 2000;**160**(6):786–794.
3. 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**(4):192–195.
4. Minagawa H, Uchitomi Y, Yamawaki S, Ishitani K. Psychiatric morbidity in terminally ill cancer patients. *A prospective study*. *Cancer* 1996;**78**(5):1131–1137.
5. Pantilat SZ. End-of-life care for the hospitalized patient. *Med Clin North Am* 2002;**86**(4):749–770, viii.
6. Casarett DJ, Inouye SK. Diagnosis and management of delirium near the end of life. *Ann Intern Med* 2001; **135**(1):32–40.
7. Gagnon P, Allard P, Masse B, DeSerres M. Delirium in terminal cancer: a prospective study using daily screening, early diagnosis, and continuous monitoring. *J Pain Symptom Manage* 2000;**19**(6):412–426.
8. 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**(3):183–194.
9. Lawlor PG, Bruera ED. Delirium in patients with advanced cancer. *Hematol Oncol Clin North Am* 2002; **16**(3):701–714.
10. Lawlor PG. The panorama of opioid-related cognitive dysfunction in patients with cancer: a critical literature appraisal. *Cancer* 2002;**94**(6):1836–1853.

Copyright © 2010 John Wiley & Sons, Ltd.

DOI: 10.1002/pon

11. Bruera E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain* 1989;**39**(1):13–16.
12. Bruera E, Fainsinger RL, Miller MJ, Kuehn N. The assessment of pain intensity in patients with cognitive failure: a preliminary report. *J Pain Symptom Manage* 1992;**7**(5):267–270.
13. Marcantonio ER, Juarez G, Goldman L *et al*. The relationship of postoperative delirium with psychoactive medications. *JAMA* 1994;**272**(19):1518–1522.
14. Schor JD, Levkoff SE, Lipsitz LA *et al*. Risk factors for delirium in hospitalized elderly. *J Am Med Assoc* 1992; **267**(6):827–831.
15. Fleishman SB, Lesko LM, Breitbart W. Treatment of organic mental disorders in cancer patients. In *Psychiatric Aspects of Symptom Management in Cancer Patients*, Breitbart W, Hollamd JC (eds). American Psychiatric Press: Washington, 1993.
16. Gagnon P, Charbonneau C, Allard P, Soulard C, Dumont S, Fillion L. Delirium in advanced cancer: a psychoeducational intervention for family caregivers. *J Palliat Care* 2002;**18**(4):253–261.
17. Leipzig RM, Goodman H, Gray G, Erle H, Reidenberg MM. Reversible, narcotic-associated mental status impairment in patients with metastatic cancer. *Pharmacology* 1987;**35**(1):47–54.
18. de Stoutz ND, Tapper M, Fainsinger RL. Reversible delirium in terminally ill patients. *J Pain Symptom Manage* 1995;**10**(3):249–253.
19. Caraceni A, Martini C, De Conno F, Ventafridda V. Organic brain syndromes and opioid administration for cancer pain. *J Pain Symptom Manage* 1994;**9**(8):527–533.
20. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. *J Pain Symptom Manage* 1995;**10**(5):378–384.
21. Inouye SK, BogardusJr ST, Charpentier PA *et al*. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med* 1999;**340**(9): 669–676.
22. Williams MA, Ward SE, Campbell EB. Confusion: testing versus observation. *J Gerontol Nurs* 1988;**14**(1):25–30.
23. Williams MA. Delirium/acute confusional states: evaluation devices in nursing. *Int Psychogeriatr* 1991;**3**(2):301–308.
24. Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. *J Pain Symptom Manage* 1995;**10**(1):35–77.
25. Oken MM, Creech RH, Tormey DC *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;**5**(6):649–655.
26. Gaudreau JD, Gagnon P. Psychotogenic drugs and delirium pathogenesis: the central role of the thalamus. *Med Hypotheses* 2005;**64**(3):471–475.
27. Dai YT, Lou MF, Yip PK, Huang GS. Risk factors and incidence of postoperative delirium in elderly Chinese patients. *Gerontology* 2000;**46**(1):28–35.
28. Gaudreau JD, Gagnon P, Harel F, Roy MA, Tremblay A. Psychoactive medications and risk of delirium in hospitalized cancer patients. *J Clin Oncol* 2005;**23**(27):6712–6718.
29. Gaudreau JD, Gagnon P, Roy MA, Harel F, Tremblay A. Association between psychoactive medications and delirium in hospitalized patients: a critical review. *Psychosomatics* 2005;**46**(4):302–316.
30. Houts PS, Rusenas I, Simmonds MA, Hufford DL. Information needs of families of cancer patients: a literature review and recommendations. *J Cancer Educ* 1991;**6**(4):255–261.
31. Pereira J, Lawlor P, Vigano A, Dorgan M, Bruera E. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J Pain Symptom Manage* 2001;**22**(2):672–687.
32. Korte W, de Stoutz N, Morant R. Day-to-day titration to initiate transdermal fentanyl in patients with cancer pain: short- and long-term experiences in a prospective study of 39 patients. *J Pain Symptom Manage* 1996; **11**(3):139–146.
33. Cherny NI, Portenoy RK. Cancer pain management. Current strategy. *Cancer* 1993;**72**(Suppl 11):3393–3415.
34. Dillon C, Lopez J, Leyba C. Oxazepam cost-savings conversion. *Hosp Pharm* 2001;**36**(6):639–644.
35. Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *Cochrane Database Syst Rev* 2007;**2**: CD005563.
36. Leung JM, Sands LP, Wang Y *et al*. Apolipoprotein E e4 allele increases the risk of early postoperative delirium in older patients undergoing noncardiac surgery. *Anesthesiology* 2007;**107**(3):406–411.
37. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg* 2006; **102**(4):1255–1266.

Copyright © 2010 John Wiley & Sons, Ltd.

DOI: 10.1002/pon