Symptom Expression in Patients with Advanced Cancer Admitted to an Acute Supportive/Palliative Care Unit With and Without Delirium

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Advanced cancer • Delirium • Memorial Delirium Assessment Scale • Palliative care • Edmonton Symptom Assessment Scale

ABSTRACT

Aim. The aim of this study was to investigate the relationship between delirium and symptom expression in patients with advanced cancer admitted to an acute supportive/palliative care unit (ASPCU).

Methods. A consecutive sample of patients with advanced cancer who were admitted to an ASPCU was prospectively assessed for a period of 10 months. The Edmonton Symptom Assessment Scale (ESAS) and the MDAS (Memorial Delirium Assessment Scale) were measured at admission (T0) and after 7 days of palliative care (T7).

Results. Two hundred forty-six patients had complete data regarding MDAS measurements, at either T0 and T7. Of these, 75 (30.5%) and 63 patients (25.6%) had delirium at T0 and after a week of palliative care (T7), with a decrease in the frequency of delirium of 4.9% (from 30.5% to 25.6%); that means that 16% of patients with delirium improved their cognitive status after initiation of palliative care. Intensities of pain, depression, poor well-being, and global ESAS were

significantly higher in patients with delirium. Patients who did not have delirium at T0 but developed delirium during admission after 1 week of palliative care had a higher level of symptom expression for pain, weakness, nausea, anxiety, dyspnea, appetite, and consequently global ESAS. Patients who did not develop delirium at any time had a relevant decrease in intensity of all ESAS items after 1 week of palliative care. The decrease of symptom intensity was significant for pain, insomnia, appetite, poor well-being, and global ESAS in patients with delirium either at T0 and T7, although these differences were less relevant than those observed in patients without delirium. In patients with delirium at T0 who improved their cognitive function at T7 (no delirium), significant changes were found in most ESAS items.

Conclusion. Symptom expression is amplified in patients with delirium, whereas patients without delirium may be more responsive to palliative treatments with a significant decrease in intensity of ESAS items. *The Oncologist* 2019;24:e358–e364

Implications for Practice: Symptom expression is amplified in patients with cancer who have delirium, whereas patients without delirium may be more responsive to palliative treatments with a significant decrease in symptom intensity.

INTRODUCTION

Delirium is a neuropsychiatric condition frequently observed in patients with advanced cancer. The underlying etiology is often multifactorial and results in significant distress not only to the patient but also to his or her family and health caregivers. Delirium adversely impacts on functional decline, increases length of hospital stay and medical

cost, is a significant cause of distress, and is associated with short survival [1–3]. Delirium is also the most frequent symptom requiring a palliative sedation both at home and in inpatient units [4–7]. This complex but common disorder in palliative care has been variably reported in literature, ranging between 13% and 88%, with a particular frequency

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at the end of life. In a previous study performed in 847 patients recruited in different palliative care settings, about 42% of patients had delirium at admission [8]. This percent increased 1 week after palliative care (about 67%), different from what occurred in an acute palliative care unit, where at discharge there was a significant decrease in the number of patients with delirium [9], possibly because of a more aggressive intervention or simply because of the earlier stage of disease.

Altered cognitive function may lead to misinterpretation of symptom assessment and may lead to inappropriate interventions. Regrettably, this neuropsychiatric disorder is often unrecognized or insufficiently diagnosed and poorly managed by clinicians [3, 10, 11]. Delirium impairs recognition of physical symptoms and complicates optimal symptom management [12, 13]. A retrospective study showed that patients who developed delirium during admission reported higher level of symptoms, particularly pain [14].

The purpose of this study was to assess whether the presence of delirium may affect the expression of specific symptoms reported by advanced cancer patients admitted to an acute palliative/supportive care unit (ASPCU), and whether such a relation changes after 1 week of palliative care.

MATERIALS AND METHODS

This is a secondary analysis of a paper assessing delirium prevalence in an ASPCU [9]. The institutional review board at the University of Palermo approved the study, and written patients' or relatives' informed consent was obtained. A consecutive sample of patients with advanced cancer who were admitted to an ASPCU was prospectively assessed for a period of 10 months. Patients who were dying, who were unable to be assessed by tools chosen in this study, or who had an expected survival of few days were excluded. All patients underwent comprehensive and continuous symptom assessment and management during their hospital stay at the unit. Delirium was defined as those patients with a score of $\geq 7/30$ according to the Memorial Delirium Assessment Scale (MDAS). MDAS is a tool frequently used in palliative care to quantify the intensity of delirium. MDAS includes different items assessing the level of consciousness, disorientation, short-term memory, digit span, attention, disorganized thinking, perceptual disturbances, delusions, psychomotor activity, and sleep-wake cycle disturbances [15]. No specific protocol was used for the management of delirium. Rather, meticulous assessment of patients and individual treatment were based on clinical monitoring, optimization of hydration, maintaining an appropriate fluid balance, correction of metabolic alterations, opioid switching, and use of antipsychotic drugs [16, 17].

Data Collection

Patients demographics, including age, gender, primary diagnosis, Karnofsky status, stage of disease, and educational level, were collected. The Edmonton Symptom Assessment Scale (ESAS) was used to assess physical and psychological symptoms at admission (T0) and 7 days after admission or

at discharge (T7) [18]. The form was filled by patients assisted by physicians. The MDAS was used to assess the cognitive status of patients and measured at the same intervals.

Statistical Analysis

Statistical analysis of quantitative and qualitative data, including descriptive statistics, was performed for all items. Continuous data are expressed as mean $\pm$ SD, unless otherwise specified. Frequency analysis was performed using Pearson's chi-square test and Fisher's exact test, as needed. The univariate analysis of variance (ANOVA) was performed to evaluate the differences in mean symptom intensity between the patient groups with and without delirium. The paired-samples Student's *t* test was used to compare the intragroup symptom intensity at the different intervals. Any missing data regarding ESAS items (<2% both T0 and T7) were excluded from statistical analysis. Data were analyzed by IBM SPSS Software 22 version (IBM Corp., Armonk, NY). All *p* values were two-sided, and *p* < .05 was considered statistically significant.

RESULTS

Of 314 admissions during the study period, 272 patients met inclusion criteria. The remaining patients died, had a short hospitalization, or did not have a MDAS assessment at T0 because they were unable to perform ESAS. The mean age was 65.6 years (SD 11.8), 157 patients were male, and the mean Karnofsky status was 47.4 (SD 10.3). The characteristics of patients, according to the levels of MDAS, are reported in Table 1. Of 272 patients who had MDAS available at T0, 86 patients (31.6%) had a diagnosis of delirium. Patients with delirium were more likely be older, male, and with a lower Karnofsky status. Values of depression and poor well-being were higher in patients with delirium (Table 1).

Two hundred forty-six patients had complete data regarding MDAS measurements, either at T0 and T7. Among 246 patients, 75 (30.5%) and 63 (25.6%) patients had delirium at T0 and after a week of palliative care (T7), with a decrease in the frequency of delirium of 4.9% (from 30.5% to 25.6%), which means that 16% of patients with delirium improved their cognitive status after initiation of palliative care.

The values of ESAS items in patients with delirium and without delirium recorded at T7 are presented in Table 2. Intensities of pain, depression, poor well-being, and global ESAS were significantly higher in patients with delirium.

Patients who did not have delirium at T0 but developed delirium during admission after 1 week of palliative care had a higher level of symptom expression for pain, weakness, nausea, anxiety, dyspnea, appetite, and consequently global ESAS (Table 3). Patients who did not develop delirium at any time had a relevant decrease in intensity of all ESAS items after 1 week of palliative care (Table 4). The decrease of symptom intensity was significant for pain, insomnia, appetite, poor well-being, and global ESAS in patients with delirium at either T0 and T7

Table 1. Comparison of demographics and clinical characteristics of patients who had delirium and those who did not have delirium at admission (T0)

Demographic or clinical characteristic	Without delirium	With delirium	<i>p</i> value
Age, mean (SD), y	64.2(11.9)	68.8(11.1)	0.003
Gender, <i>n</i>			0.001
Female	91	24	
Male	95	62	
Karnofsky, mean (SD)	49.3(9.9)	43.5(10.1)	<0.0005
Primary tumor, <i>n</i>			0.310
Lung	32	23	
Breast	38	9	
Genitourinary	26	16	
Gastrointestinal	30	8	
Liver	11	6	
Pancreas	10	5	
Head–neck	7	3	
Unknown	9	2	
Hematologic disease	13	8	
Other	10	6	
ESAS, mean (SD)			
Pain	5.3 (2.9)	5.2 (2.9)	0.733
Weakness	5.8 (2.8)	5.6 (2.8)	0.577
Nausea	2.2 (2.5)	1.8 (2.6)	0.374
Depression	3.0 (2.9)	3.9 (3.2)	0.045
Anxiety	2.8 (3.0)	3.4 (3.3)	0.144
Drowsiness	4.3 (2.6)	4.3 (3.0)	0.825
Dyspnea	2.3 (3.2)	2.9 (3.3)	0.164
Insomnia	4.3 (3.3)	4.9 (3.4)	0.139
Appetite	4.7 (3.1)	4.8 (3.5)	0.680
Poor well-being	5.6 (2.4)	6.7 (2.0)	0.001
Global ESAS	39.8 (16.3)	41.0 (18.6)	0.594

Abbreviation: ESAS, Edmonton Symptom Assessment Scale.

Table 2. Comparison of ESAS items in patients with and without delirium 7 days after admission

ESAS item	Without delirium	With delirium	<i>p</i> value
Pain	2.4 (1.6)	3.1 (2.1)	0.029
Weakness	2.9 (2.4)	3.9 (2.2)	0.014
Nausea	0.8 (1.7)	1.2 (2.3)	0.121
Depression	1.4 (1.8)	2.5 (2.2)	0.010
Anxiety	1.6 (2.4)	2.2 (2.6)	0.130
Drowsiness	2.4 (2.3)	3.5 (2.6)	0.008
Dyspnea	1.1 (2.0)	2.0 (2.1)	0.042
Insomnia	2.4 (2.6)	3.1 (2.9)	0.065
Appetite	2.7 (2.5)	3.6 (2.8)	0.088
Poor well-being	3.3 (2.0)	4.3 (2.1)	0.037
Global ESAS	21 (13.9)	27.1 (18.2)	0.006

Mean data adjusted for baseline values. Abbreviation: ESAS, Edmonton Symptom Assessment Scale.

(Table 5), although these differences were less relevant than those observed in patients without delirium. The changes in ESAS items in patients with delirium at T0 who improved their cognitive function at T7 (no delirium) are

reported in Table 6. Significant changes were found in most ESAS items, including pain, weakness, depression, anxiety, insomnia, and poor well-being, as well as global ESAS.

Table 3. Patients without delirium at T0, who developed delirium during admission after 1 week of palliative care (10 patients)

Symptom	Without delirium at T0	Delirium at T7	Mean difference	p value
Pain	6.4 (2.6)	2.6 (1.2)	3.7 (2.4)	0.002
Weakness	7.8 (2.4)	3.8 (3.0)	4.0 (4.1)	0.020
Nausea	3.5 (3.6)	1.2 (1.9)	2.3 (2.9)	0.045
Depression	3.4 (3.6)	1.5 (1.8)	1.8 (4.4)	0.234
Anxiety	3.6 (3.4)	0.6 (1.4)	3.0 (3.7)	0.044
Drowsiness	5.7 (2.9)	4.1 (2.8)	1.6 (3.1)	0.153
Dyspnea	3.8 (4.2)	1.7 (2.7)	2.1 (2.7)	0.048
Insomnia	5.2 (3.6)	3.7 (3.9)	1.4 (2.6)	0.141
Appetite	6.3 (3.3)	3.1 (2.5)	3.2 (2.9)	0.011
Poor well-being	6.8 (2.3)	5.2 (2.7)	1.6 (2.6)	0.129
Global ESAS	50.3 (21.8)	25.5 (16.0)	24.8 (19.7)	0.003

Abbreviations: ESAS, Edmonton Symptom Assessment Scale; T0, time of admission; T7, 7 days after admission.

Table 4. Patients delirium-free at admission and after 1 week of palliative care (*n* = 161)

Symptom	No delirium at T0	No delirium at T7	Mean difference	p value
Pain	5.2 (2.8)	2.4 (1.8)	2.8 (2.9)	0.000
Weakness	5.6 (2.8)	2.9 (2.5)	2.6 (3.0)	0.000
Nausea	2.0 (2.8)	0.7 (1.6)	1.3 (3.1)	0.000
Depression	2.9 (2.9)	1.4 (2.0)	1.41 (2.7)	0.000
Anxiety	2.7 (2.9)	1.5 (2.2)	1.1 (2.9)	0.000
Drowsiness	4.0 (2.5)	2.4 (2.3)	1.5 (3.0)	0.000
Dyspnea	2.0 (3.0)	1.0 (2.1)	0.9 (2.9)	0.000
Insomnia	4.3 (3.3)	2.4 (2.5)	1.8 (3.4)	0.000
Appetite	4.5 (3.1)	2.7 (2.6)	1.8 (3.5)	0.000
Poor well-being	5.5 (2.3)	3.2 (2.0)	2.2 (2.5)	0.000
Global ESAS	38.5 (15.6)	20.6 (13.0)	17.8 (16.5)	0.000

Abbreviations: ESAS, Edmonton Symptom Assessment Scale; T0, time of admission; T7, 7 days after admission.

Table 5. Patients with delirium at T0 and at T7 (53 patients)

Symptom	Delirium at T0	Delirium at T7	Mean difference	p value
Pain	4.8 (2.8)	3.1 (2.4)	1.7 (2.5)	0.000
Weakness	5.2 (2.84)	3.9 (2.7)	1.3 (3.4)	0.010
Nausea	1.5 (2.2)	1.2 (2.2)	0.3 (2.6)	0.437
Depression	3.8 (3.1)	2.6 (2.8)	1.1 (3.3)	0.017
Anxiety	3.2 (3.1)	2.5 (2.8)	0.7 (3.2)	0.112
Drowsiness	3.9 (3.0)	3.4 (3.0)	0.5 (3.7)	0.343
Dyspnea	2.9 (3.2)	2.1 (2.5)	0.8 (3.3)	0.091
Insomnia	4.3 (3.2)	3.0 (3.1)	1.3 (4.2)	0.040
Appetite	5.0 (3.3)	3.6 (3.1)	1.3 (3.1)	0.007
Poor well-being	6.6 (2.2)	4.1 (2.5)	2.5 (3.0)	0.000
Global ESAS	39.2 (18.2)	27.4 (18.7)	11.8 (20.7)	0.000

Abbreviations: ESAS, Edmonton Symptom Assessment Scale; T0, time of admission; T7, 7 days after admission.

DISCUSSION

Analysis of these data showed that patients admitted to an ASPCU presenting delirium had a lower Karnofsky status,

were older and more likely to be male, and reported an overall worse symptom burden compared with those who did not have delirium, particularly depression and poor

Table 6. Patients with delirium at T0 and without delirium at T7 (22 patients)

Symptom	Delirium at T0	No delirium at T7	Mean difference	p value
Pain	5.8 (2.6)	2.7 (2.0)	3.0 (2.6)	0.000
Weakness	6.1 (2.7)	3.3 (2.5)	2.8 (2.4)	0.000
Nausea	1.5 (2.1)	1.4 (2.5)	0.1 (1.8)	0.727
Depression	3.8 (3.5)	1.3 (1.7)	2.4 (3.0)	0.001
Anxiety	3.8 (3.4)	1.7 (1.9)	2.0 (3.3)	0.008
Drowsiness	4.0 (2.9)	2.6 (2.0)	1.4 (3.4)	0.071
Dyspnea	2.8 (3.2)	1.5 (1.8)	1.2 (3.5)	0.109
Insomnia	5.4 (3.1)	2.3 (2.6)	3.1 (3.1)	0.000
Appetite	4.2 (3.4)	2.7 (2.2)	1.5 (3.4)	0.052
Poor well-being	6.8 (1.5)	3.7 (1.7)	3.0 (2.1)	0.000
Global ESAS	44.3 (16.5)	23.6 (13.4)	20.6 (14.0)	0.000

Abbreviations: ESAS, Edmonton Symptom Assessment Scale; T0, time of admission; T7, 7 days after admission.

well-being. Of interest, patients who did not have delirium at admission but developed delirium during admission presented an even higher level of symptom overexpression, including pain, weakness, nausea, anxiety, dyspnea, poor appetite, and, as a consequence, global ESAS. Analysis of subcategories demonstrated that symptom control after palliative care was highly effective in patients without delirium and partially effective in patients with delirium at both assessment points. Globally, these data suggest that delirium is a frequent factor in patients with advanced cancer admitted to an ASPCU, able to overexpress symptom burden, and that these patients can be more difficult to treat with a palliative care intervention. Although delirium may be reduced by optimal adjustment of medication with a careful assessment and available therapies, its persistence in nonresponders seems to increase the level of symptom expression. The occurrence of delirium after admission suggests a general deterioration with a broader symptom burden. This data is consistent with a previous study in which patients who developed delirium after admission had a lower rate of delirium reversal and shorter survival [19]. In a recent retrospective study, patients who developed delirium during admission reported higher levels of depression, anxiety, appetite, well-being, and sleep. A decrease in delirium was associated with an improvement in symptom intensity [14]. In particular, pain was constantly overexpressed. However, patients' selection and assessment points were different from those chosen in this study. Only patients who did not have a diagnosis of delirium at the time of admission were eligible for the study. For patients who developed delirium, follow-up ESAS was collected within 3 days, and for patients without delirium, follow-up ESAS was collected 3 days before discharge from the acute palliative care unit. In the present study, patients were selected in a different way: those who had delirium or not at admission followed by a palliative care intervention. On the other hand, in patients who did not have delirium at admission or during admission up to discharge, optimization of medications allowed a more relevant decrease in reported symptom intensity, suggesting that delirium may be an impediment to achieving the goal of symptom control.

From a clinical perspective, patients with delirium may be at risk of opioid dose escalation or use of other adjuvants or other symptomatic drugs, which can then worsen delirium in a negative circuit. Alternately, pain itself may induce delirium. The treatment should be carefully evaluated for the obvious clinical implications, which requires a high level of expertise. This observation calls for a constant and adequate assessment of delirium. Although some patients present clear signs of delirium because they are confused and/or agitated, and symptom assessment is unlikely for their condition, those who are able to express their symptoms, although inappropriately, are more likely to be misinterpreted by a clinician. It has been found that in about 60% of consultations, delirium was missed by the primary referring team [3]. Thus, missed delirium is a confounding factor that can lead to inappropriate intervention.

It has been hypothesized that increased symptom expression in the presence of delirium is due to an imbalance between a low cholinergic and an excess dopaminergic state [20, 21]. Several neurotransmitters, including GABA and serotonin, may also affect the activity of both pathways [22]. The reduction of the GABA inhibitory activity seems to be determinant in the process of disinhibition of distress, and patients may also appear more anxious or agitated [23].

In patients with advanced cancer, delirium is a common occurrence; it is not necessarily due to medications or biochemical changes but can be a natural consequence of general derangement in last days or weeks of life. The finding of worsening symptom expression in patients with delirium suggests that multiple assessment tools are necessary to decode the clinical expression of patients with advanced cancer. Although delirium is the consequence of multiple etiologies, no specific protocol can be used, according to the principal presumed mechanism. The better way to proceed is by incorporating all information available to make an appropriate assessment and recognition of the patient's status, and intervening accordingly. In this sense, information gathered from caregivers is of paramount importance.

There are several study limitations. This was a secondary analysis of a study performed for other purposes. The

lower rate of delirium found in patients admitted to an ASPCU is attributable to the admission criteria according to the earlier supportive care pathway adopted in this unit, where patients have a longer life expectancy [17] attested by a lower mortality rate (range, 3%-7%) [16, 17]. Upon admission to an ASPCU, intensive efforts to remove reversible factors that can determine delirium, such as drugs, electrolyte abnormalities, or other metabolic issues, are more likely to be performed in comparison with patients admitted to hospice or home care who have a late referral to palliative care and a limited survival expectancy (in Italy about 30 days) [8, 24, 25]. In a large sample of patients recruited in home care and hospice settings, only 30% of patients were available even for a simple assessment, as most of them were severely ill, suggesting a late referral to standard palliative care services. This is confirmed by a consistent number of patients who developed delirium after starting home care or hospice care [8]. In these cases, delirium could more frequently be due to a general derangement observed in the last weeks of life, rather than to reversible causes. In this study, many patients were still receiving active treatments when admitted, although survival information was not available, because of the high rate of discharge to other settings [17]. Although dying patients were not included in this study, the number of these patients is negligible in this kind of unit and should not infer with global data. Moreover, the palliative care treatment was individually based to find the best solution in a specific clinical condition, rather than using a specific protocol. The intent of this study, in fact, was not to evaluate the efficacy of a specific treatment. Treatment of delirium requires a broader approach rather than a specific drug. The information gathered in this study better reflects the real world of a dedicated unit where particular attention is paid to assessment and best supportive care is ensured by a high level of clinical and research experience.

Another limitation could be the single-unit experience and a lack of comparison with other settings. On the other hand, data were prospectively and longitudinally collected with two time points, at admission and after a comprehensive palliative care intervention. A week's interval is reasonably considered a sufficient time for having a clinical response. Finally, the ESAS record was performed by patients assisted by clinicians, considering the purpose of the study.

CONCLUSION

The study showed that patients admitted to APCSU with delirium reported higher distress in pain and depression and that patients who subsequently developed delirium after a week presented an even higher expression of multiple symptoms. Indeed, the symptom improvement of patients who did not have delirium at admission and after a palliative intervention was relevant. Screening patients with advanced cancer and severe symptom intensity for delirium should be mandatory. Other data from other settings or with multicenter studies should be gathered to confirm this observation reported in an ASPCU.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

The authors indicated no financial relationships.

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