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General and Supportive Care

Comprehensive approaches to managing delirium in patients with advanced cancer

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SUMMARY

Delirium is a frequently under-recognized complication in patients with advanced cancer. Uncontrolled delirium eventually leads to significant distress to patients and their families. However, delirium episodes can be reversed in half of these patients by eliminating precipitating factors and using appropriate interventions. The purpose of this narrative review is to discuss the most recent updates in the literature on the management of delirium in patients with advanced cancer. This article addresses the epidemiology, cause, pathophysiology, clinical characteristics, and assessment of delirium as well as various treatment options, including nonpharmacologic intervention and palliative sedation.

Introduction

Delirium is one of the most frequent and distressing complications seen in patients with advanced cancer. Family caregivers experience high levels of distress from caring for delirious patients with terminal illness. Moreover, studies have shown that many patients who experienced a delirium episode recalled it vividly and rated it as a moderately to severely stressful experience.[1,2]

Delirium impairs the communication ability of patients with advanced cancer and subsequently interferes with the appropriate assessment of physical symptoms such as pain. Delirium increases the duration of hospitalization and the risk for hospital-acquired complications. Delirium is also a negative prognostic indicator for survival in advanced cancer patients.[3,4] Thus, the proper management of delirium can be a challenging issue for physicians. The purpose of this review is to present a clinical update of the symptoms of delirium in advanced cancer patients and to discuss comprehensive approaches to managing delirium, including pharmacologic and nonpharmacologic interventions and palliative sedation.

Definition and incidences

Delirium is not a disease but a clinical syndrome arising from multiple causes with similar symptoms. Delirium is a global brain dysfunction characterized by acute disruption of attention and cognition but without permanent organic changes in the brain; therefore, delirium may be reversible even in patients with terminal cancer.[5]

Delirium can be defined as a mental state in which a person is confused, disoriented, and unable to think or remember clearly.[6] However, the characterization of delirium has evolved from a list of multiple symptoms to two imperative components, disordered attention and cognition.[7] The American Psychiatric Association issued diagnostic criteria for delirium in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*)-*III*, and those criteria have evolved into DSM-IV over the years.[8–10] The *DSM-IV* defines delirium as a disturbance of consciousness with inattention and problems in cognition and/or a disturbance in perception that develop over hours to days with organic causes.[10,11] Confusion is often used as a general term for incoherent thinking, and it is an essential component of delirium in terms of disordered cognition. Confused patients have problems thinking with normal speed, clarity, or coherence. Clinical diagnosis of delirium usually has been reserved for patients with obvious manifestation of disorientation and confusion. This clinical practice can cause mild delirium to be overlooked. However, there is no direct evidence that universal screening in asymptomatic individuals can directly improve patient outcomes.[12]

The definitions of prevalence and incidence for delirium and should be differentiated. Prevalence defines the number of cases of delirium that are present in a population at a specified time, whereas incidence represents the occurrence rate of delirium during a certain period in a population at risk. Many studies of delirium describe its prevalence at baseline and the incidence of new cases during the study period such as during hospitalization.

The incidence of delirium in patients with advanced cancer ranges from 6% to 68% depending on the health care setting, diagnostic tool, and disease status of the population (Table 1).[13–19]

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Table 1
Incidence of delirium in advanced cancer patients.

	Incidence (No.)	Sample size (No.)	Study design	Diagnostic tool	Admitted health setting
Chun-Kai et al.[13]	46.9% (107)	228	Prospective	DRS	Hospice and palliative care
Kim et al.[14]	30.2% (33)	108	Prospective	CAM	Palliative care
Gaudreau et al.[15]	30.0% (31)	107	Prospective	Nu-DESC	Oncology unit
Gagnon et al.[16]	6.2% (N/A)	2515	Prospective	CRS	Palliative care
Weckmann[17]	38.6% (17)	44	Retrospective	N/A	Academic medical center
Lawlor et al.[18]	68.3% (71)	104	Prospective	MDAS	Palliative care
Gagnon et al.[19]	32.8% (21)	64	Prospective	CAM	Hospice

CAM, Confusion Assessment Method; DRS, Delirium Rating Scale; MDAS, Memorial Delirium Assessment Scale; Nu-DESC, Nursing Delirium Screening Scale; N/A, not available; CRS, Confusion Rating Scale.

The frequency increases up to 90% in cancer patients near the end of life.[20] The frequency of delirium in outpatient clinics is little known. One small study reported that the incidence and prevalence of delirium were 45% and 7%, respectively, during outpatient treatment for head and neck cancer.[21] However, delirium is often misunderstood or misdiagnosed as anxiety disorder or depression.[22] Thus, the incidence or prevalence may be underreported.

Precipitating factors and pathophysiology

Delirium is caused by diverse factors that present as global cerebral dysfunction. To prevent delirium, a balance is normally maintained between the inhibitory system and predisposing and precipitating factors for delirium. When these predisposing and precipitating factors disturb that balance, delirium can occur. Patients with multiple predisposing conditions are more vulnerable to the precipitating factors than are patients with only one predisposing factor.[23] For example, elderly patients have a high prevalence of dementia and commonly have other coexisting conditions such as cancer. Patients who have had multiple chemotherapy regimens or cancer progression could also be more likely to experience delirium from minor factors such as hypnotics.[24]

Cancer is particularly common in the elderly population, and cancer and old age are major predisposing conditions for delirium. Thus, many elderly patients with cancer, especially those with advanced-stage disease, are highly vulnerable to and can easily develop delirium from minor precipitating factors. Precipitating factors for delirium include constipation, dehydration, hypoxia, immobility, infection, uncontrolled pain, bladder catheterization or outlet obstruction, and several medications—especially benzodiazepine or meperidine. The utilization of the acronym CHIMBOP (constipation, hypovolemia/hypoglycemia, infection, medications, bladder catheter/bladder outlet obstruction, oxygen deficiency, pain) can help medical staff to remember multiple precipitating factors.[25]

The mechanism that causes delirium is poorly understood, and only hypothetical models exist. The two prevailing theories for delirium pathophysiology are neurotransmitter imbalance characterized by acetylcholine (Ach) deficiency and unbalanced inflammatory response.[26–28]

Neurotransmitters involving development of delirium include Ach, dopamine, serotonin, and γ-aminobutyric acid (GABA).[29] Of these, Ach—which is involved in normal attention, memory, and arousal—is believed to be a key neurotransmitter in the final common pathway in the development of delirium. Dopamine and serotonin are another important neurotransmitters for attention and cognition. Activation of dopamine subreceptors (D2–D4) induces decreased Ach secretion, whereas serotonin is associated with secretion of Ach by interacting with the cholinergic and dopaminergic system.[30]

Any medical conditions that decrease cholinergic activity or increase dopamine production may result in delirium.[26] For example, hypoxemia, infection, dehydration, and electrolyte imbalance commonly occur in advanced cancer patients and can be precipitating factors for delirium. In addition, polypharmacy and psychoactive medications such as opioids, benzodiazepines, and serotonin antagonists are widely used for supportive care and can influence the production of causative neurotransmitters in advanced cancer patients.[31] Studies have shown that opioids, corticosteroids, or benzodiazepines are associated with increased risk of delirium in hospitalized cancer patients.[15,32]

According to the unbalanced inflammatory response model, cytokines from acute systemic inflammation also contribute to delirium. Among these are proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, which are produced in the peripheral blood during infection.[33] These peripheral cytokines can be transmitted to the brain and induce the activation of microglia, which subsequently create a neurotoxic response and eventually lead to delirium. The microglial response is normally under strict control of cholinergic inhibitory system.[34] van Gool et al. suggested that impaired cholinergic inhibitory control of microglia in vulnerable patients contributes to uncontrolled neuroinflammation and ultimately causes delirium.[35]

Recent studies suggested that cortisol may also have a role in the development of delirium.[36] Stress triggers the hypothalamic–pituitary–adrenal (HPA) axis and elicits production of cortisol. Repetitive and chronic stresses such as cancer could cause disruption of HPA axis homeostasis. It is hypothesized that cortisol, when secreted excessively and circulated in the blood at high levels, has harmful effects on hippocampal activity and results in cognitive dysfunction.

Clinical characteristics

Disturbance of attention with abnormal consciousness and cognition are two key features needed to establish a diagnosis of delirium by *DSM-IV* criteria.[11] The pace of symptom occurrence is important for differentiating from dementia. Delirium has an acute and rapid onset, whereas dementia develops more gradually.[37] The severities of delirium's symptoms are not constant but rather wax and wane over a 24-h period with characteristic lucid intervals. For example, patients tend to be disoriented in the evening and become lucid the following morning. Delirium may present as complaints of fatigue, sleep disturbance, disinterest, and hypersensitivity to environment. Thus, physicians or nurses should be vigilant for early behavior changes indicating delirium and perform a clinical assessment to confirm the delirium. The clinical features of delirium are shown in Table 2.

Disturbance of attention and consciousness

Disturbance of consciousness means that patients have a problem in their wakefulness or arousal. Such patients can be hypoalert or hyperalert, with mental statuses ranging from coma to hyperalertness marked by excess sensitivity to environmental stimuli and being easily startled.