

Short Communication

## About Delirium in Cancer Patients

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Cancer diseases affect approximately 10 million people only in Europe. As a result of the demographic development, their prevalence is expected to double during the next 10 years. Cancer accounted for nearly ten million deaths worldwide in 2020, or nearly 1 in 6 deaths. Meanwhile the number of survivors continues to grow, not just because of earlier detection and treatment, but also because of revolutionary new therapies. This changes the landscape from a terminal illness to more of a chronic illness. Such perspective on neoplasms has broadened the scope of care from treating the disease alone to managing cancer-related symptoms at different stages of the disease trajectory including mental disorders.

On psychiatric consultation of 546 cancer patients there was revealed that 54% of the referrals were diagnosed as having adjustment disorders, 15% delirium and 9% major depression [1]. The results showed elevated risk of comorbid common mental health disorders among persons who at the time of the study were undergoing treatment for cancer across all countries studied compared with either cancer survivors or cancer-free respondents.

For patients, caregivers, and families, going through cancer can be a devastating experience with many stresses and emotional upheavals.

Cancer patients often have delirium particularly ones with far-advanced disease. The term *delirium* derives from the Latin word *delirare* (*lira* is Latin for "furrow or track" and the prefix *de* means "down, out of, or away"), which means to deviate from a straight line or "out of the furrow" [2].

This syndrome an often fatal problem affecting up to 50% of hospitalized seniors, and costing over \$182 billion (2011) per year in 18 European countries [4]. This disorder is included on the patient safety agenda [5] and has been increasingly targeted as an indicator of healthcare quality for seniors.

Delirium has been defined as a disorder of global cerebral function characterized by disordered awareness, attention, and cognition. Its occurrence rates range from 28% to 48% in patients with advanced cancer on admission to hospital or hospice. Variability in reported rates and clinical outcomes most likely reflects sampling from different clinical settings or different stages in the clinical trajectory of cancer, in addition to inconsistency in diagnostic terminology. Elderly patients who develop delirium during a hospitalization have an estimated 22% to 76% chance of dying during that admission.

The delirium results from inter-relationship between organism's *loci minoris resistentiae* with multiple predisposing or precipitating factors.

These factors include:

- The direct impact of cancer on the central nervous system (CNS). The systemic inflammatory response may result in a cascade of local (brain) neuroinflammation triggered by inflammatory cytokines, leading to endothelial activation, and neuronal apoptosis. Correlation between levels of circulating cytokines at diagnosis and specific types of cognitive dysfunction.
- The indirect CNS effects and paraneoplastic syndromes.

The risk factors of delirium have been identified in general medical patients (some of them with cancer) and include severe illness, level of comorbidity, advanced age, prior dementia, hypoalbuminemia, infection, azotemia, and psychoactive medications. It is likely that the quest for a single cause or mechanism for delirium will remain unanswered.

Interacting biological factors result in disruption of large-scale neuronal networks in the brain with subsequent cognitive impairment. Among these factors neurotransmitters, inflammation, physiologic stressors, metabolic derangements, electrolyte and genetic disorders are mentioned.

For many patients with delirium, it seems to be best to think about it as a manifestation of frailty, cognitive impairment, vision or hearing impairment, and comorbidity. In this context, delirium may serve as a marker of the vulnerable brain with diminished reserve capacity. Less than 10% of patients with a PS of 0-2 were diagnosed as having delirium, as opposed to more than 40% of patients with a PS of  $\geq 3$ . Delirium is typically the manifestation of a severe cerebral disorder in a vulnerable patient, subjected to noxious insults or precipitating factors. Older adults are frail when they have several problems that give rise to a loss of redundancy in their homeostatic capacity and, thus, an inability to withstand stress [6].

The delirium presentation involves a variety of neuropsychiatric symptoms common to other psychiatric disorders. This syndrome is accompanied with neurologic abnormalities, e.g. cortical, motor and electroencephalogram ones [3]. The diagnosis of delirium should be suspected in any cancer patient with demonstrating an acute onset of agitation or uncooperative behavior, personality change, cognitive disorders, fluctuating level of consciousness, or uncharacteristic anxiety or depression. This diagnosis is frequently missed and poorly documented.

Its core clinical criteria:

1. The reduced clarity of awareness and attention deficit.
2. Acuity of onset and fluctuation over the course of the day.
3. The presence of an underlying cause such as a general medical condition (e.g., hypoxia or electrolyte disturbance), medication, a combination of etiologies, or indeterminate etiology.

Other associated noncore clinical criteria features include sleep-wake cycle disturbance, delusions, emotional lability, and disturbance of psychomotor activity. The latter forms the basis of classifying delirium into three different subtypes:

1. Hypoactive that generally been found to occur with hypoxia, metabolic disturbances, and anticholinergic medications.
2. Hyperactive that is correlated with drug intoxication, or medication adverse effects.
3. Mixed, with both hypoactive and hyperactive features.

It's hypoactive type that has higher rates of incidence and mortality in patients with far-advanced cancer. Delirium presenting with hypoactive subtype, irreversible etiologies, and greater cognitive impairment is often associated with death within a period of days to weeks.

The delirium usually interferes with the recognition and control of symptoms such as pain. Uncontrolled pain can cause agitation, however, in the presence of a clear sensorium, delirium is an unlikely explanation. Patients with delirium use a significantly greater number of "breakthrough" doses of opioids at night compared with patients without delirium due to sleep wakefulness cycle reversal. As a rule, medical staff and family members attribute a functional cause to some of the early, prodromal, and more subtle signs of delir-

ium, e.g. restlessness, emotional lability. Failure to recognize delirium is particularly likely if the patient is encountered in a transient lucid phase that is part of the fluctuating nature of delirium.

Delirium and dementia have some shared clinical features such as disorientation and impairment of memory, thinking, and judgment. In elderly patients with cancer, delirium is often superimposed on dementia, giving rise to a particularly difficult diagnostic challenge. The diagnosis is more apparent when some features of delirium, especially cognitive impairment, persist. Dementia typically appears in relatively alert individuals; disturbance of consciousness is not a common feature.

Regular cognitive screening facilitates the diagnosis of delirium in cancer patients. Instruments that have favorable psychometric properties and are brief enough to allow repeated administration in cancer patients include:

The Mini-Mental State Examination (MMSE) screens for cognitive impairment and requires active patient participation in assessment.

The Confusion Assessment Method (CAM) screens for cognitive impairment but does not require formal patient participation.

The Memorial Delirium Assessment Scale (MDAS) has been validated as having diagnostic and severity rating potential. This scale allows prorating of scores when a patient cannot actively participate in testing for reasons such as dyspnea or fatigue.

In families delirium seriously challenges the ability to grant a loved one's wish to die at home; it is distressing for all concerned. Determining and securing the best care setting for the dying patient with delirium is complex. Delirium associates with the impending death, but many episodes of delirium are reversible; such reversal is consistent with the goals of care. The standard management approach in these patients is to search for and treat the reversible precipitants of delirium. Studies in patients with earlier stages of advanced cancer have demonstrated the potential utility of a thorough diagnostic assessment. 68% of delirious cancer patients experienced improved symptoms upon discovery of an etiology and institution of treatment. Delirium was more likely to reverse when dehydration could be corrected and when opioids or psychoactive medications were reduced or discontinued if possible. Irreversibility of delirium was associated with major organ failure and hypoxic encephalopathy. Reversibility of delirium was highly dependent on the etiology: hypercalcemia was judged reversible in 38%; medications in 37%; infection in 12%; and hepatic failure, hypoxia, disseminated intravascular coagulation, and dehydration each in less than 10% [7].

There is evidence that nonpharmacological interventions to management may result in faster improvement in delirium and slower deterioration in cognition, although no effects on mortality compared with usual care. Such interventions include oxygen delivery, fluid and electrolyte administration, ensuring bowel and bladder function, nutrition, mobilization, pain treatment, frequent orientation, use of visual and hearing aids, and environmental modifications to enhance a sense of familiarity.

Generally recognized standard of care for delirium's prevention and treatment is multicomponent. Revocation of drugs, besides necessary ones, treating the symptoms of delirium and metabolic disorders, providing a safe environment open the list of priorities. Medications that provoke delirium are well-known, e.g. corticosteroids, chemotherapeutic and anticholinergic agents, biological response modifiers, antidepressants, benzodiazepines, opioids. In a small trial of 20 cancer patients who developed delirium while being treated with morphine, rotation to fentanyl reduced delirium and improved pain control in 18 patients.

Treatment with antipsychotic medications is often essential to control the symptoms of delirium. Meanwhile, only 17% of terminally ill delirious patients receive any antipsychotic drugs [8]. No medications have been approved by the US FDA for treatment of this syndrome.

The neuroleptic haloperidol is recognized the drug of choice for the treatment of delirium in the patients with cancer due to its efficacy, relative safety, and versatility (e.g., few anticholinergic effects, minimal cardiovascular adverse effects, lack of active metabolites, and availability in different routes of administration. Consensus guidelines recommended initial doses in the range of 1 to 2 mg every 2 to 4 hours as needed (to 4 mg orally, intravenously, or subcutaneously) and lower starting doses, such as 0.5 mg every 4 hours as needed, in elderly patients.

The alternative options are atypical antipsychotics, the conventional medications are risperidone and olanzapine. The first one (in oral tablet and liquid formulations) has fewer extrapyramidal side effects than haloperidol; dosing begins at 1 to 2 mg per day in two divided daily doses that are titrated, if necessary, to a total dose of 4 to 6 mg per day.

Olanzapine, another atypical antipsychotic oral formulation is used with an initial dose range of 2.5 to 10 mg and a mean of 3 mg per dose in two daily doses to 20 mg orally at night. It's also reported to have antiemetic and analgesic actions.

Lorazepam (0.5-1 mg orally or parenterally) is used along with haloperidol in patients with delirium who are particularly sensitive to extrapyramidal side effects. Another exception is midazolam, a very short-acting benzodiazepine, which is given by continuous subcutaneous or intravenous infusion in doses ranging from 30 to 100 mg over 24 hours.

Midazolam is used to achieve deep sedation, especially in a terminal hyperactive or mixed delirium when agitation is refractory to other treatments. Therapeutic intervention results in delirium reversal, or at least improvement, in 30% to 75% of episodes.

There's need to protect patients from accidents or self-injury while they are restless or agitated. The use of restraints is controversial; other strategies include having family members or sitters at the bedside to prevent harm.

In the last days of life, the ideal goal of delirium management is a patient who is comfortable, not in pain, awake, alert, calm, cognitively intact, and able to communicate coherently with family and staff. When delirium is a consequence of the dying process, the goal of care may shift to providing comfort through the judicious use of sedatives, even at the expense of alertness.

Before undertaking interventions such as midazolam or propofol infusions, the clinician must describe the optimal achievable goals of therapy as they currently exist. A discussion with the family (and the patient if he/she appears to have the capacity during lucid moments) helps to elicit concerns and wishes for the type of care that best honors a desire to provide comfort and symptom control during the dying process but without death hastening. Family members should also be told to anticipate that sedation may result in a premature sense of loss and that they may feel their loved one is in some sort of limbo state, not yet dead, but no longer alive in the vital sense.

Thus, psychosocial and psycho-oncological support services considerably contribute to improving the quality of life of patients as a central outcome criterion of oncological care. Some people may not want or require support or treatment, others will be able to self-manage, and some may have more complex needs that require more intensive follow-up and support. At diagnosis, the psychological health of patients should be considered alongside their physical health and sources of support offered. Needs and symptoms may also change over time. Being mentally aware is a preference reiterated by seriously ill patients.

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