



Special Article

Management of Physical Symptoms in Patients with Advanced Cancer during the Last Weeks and Days of Life

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Patients with advanced cancer are faced with many devastating symptoms in the last weeks and days of life, such as pain, delirium, dyspnea, bronchial hypersecretions (death rattle), and intractable seizures. Symptom management in the last weeks of life can be particularly challenging because of the high prevalence of delirium complicating symptom assessment, high symptom expression secondary to psychosocial and spiritual factors, limited life-expectancy requiring special considerations for prognosis-based decision-making, and distressed caregivers. There is a paucity of research involving patients in the last weeks of life, contributing to substantial variations in clinical practice. In this narrative review, we shall review the existing literature and provide a practical approach to in-patient management of several of the most distressing physical symptoms in the last weeks to days of life.

Key words Palliative care, Cancer pain, Delirium, Dyspnea, Bronchial hypersecretions (death rattle), Seizures, Last weeks to days of life, Death, Terminal care, Palliative care unit

Introduction

As patients with advanced cancer approach the end-of-life (EOL) (i.e., last weeks to days), they often suffer from devastating physical and psychological symptoms [1,2]. These may include, but are not limited to, intractable pain, agitated delirium, and severe dyspnea, which can lead to immense suffering in terminally ill patients with cancer. Many symptoms remain under-recognized and under-treated in the last months of life, and often increase in intensity as patients approach death [3-5].

Symptom control in the last weeks of life requires certain considerations. First, symptom assessment is often complicated by delirium and/or drowsiness. Second, symptom expression may be modulated by many unique factors that have relevance in the last days of life. For example, existential distress may increase symptom expression. Third, treatment decision making is highly dependent on patient survival and their expressed wishes. For example, a patient with depression may benefit from starting methylphenidate rather than antidepressants if they have an expected survival of a few weeks only. Fourth, caregiver distress is closely associated with patient's level of distress [6]. Support for and close coordination with caregivers is paramount to optimizing patient care.

Clinicians looking after patients with advanced cancer in the last weeks to days of life need to be skilled in the manage-

ment of these complex issues. Availability of a specialized interdisciplinary palliative care team is crucial. The team may provide care in the mobile consultation team setting or in palliative care unit (PCU). PCUs are particularly important because they offer intensive symptom management and care planning by a team of highly skilled palliative care professionals. These units are different from inpatient hospice facilities which are community-based; patients with a prognosis more than 6 months can be admitted to a PCU in a hospital setting for the management of physical, psychosocial, and spiritual distress [7-9].

In this narrative review, we aim to provide an update on in-patient management of several of the most distressing physical symptoms occurring commonly in the last weeks to days of life, including pain, delirium, dyspnea, bronchial hypersecretions (death rattle) and intractable seizures. Other aspects of EOL care, such as psychosocial and spiritual issues and prognostication are covered in other articles in this issue. It should be recognized that there is a paucity of research studies specifically examining issues in the last weeks and days of life, with one literature review reporting that only 13% of palliative care studies involved patients in the last month of life [10]. This is related to many unique challenges in this setting, such as frailty in dying patients, difficulty with symptom assessment, delirium, rapidly changing health status, limited funding, and few palliative care researchers. Thus, many of the current practice patterns

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are partially based on data derived from patients earlier in the disease trajectory (e.g., pain management), recognizing much more research is needed to strengthen the body of evidence.

Cancer Pain

Pain is one of the most common concerns in patients with cancer, affecting approximately 65%-74% of patients with advanced disease and over 90% in some studies [11-13]. Sub-optimally controlled pain can have a negative impact on mood and quality of life. The concept of total pain is particularly important for patients in the last weeks to days of life, given the high prevalence of psychological issues, spiritual crisis, delirium, and caregiver distress that may all exacerbate pain expression [14,15]. The gold standard for pain assessment is patient reported outcome [16,17]. Details of pain assessment and associated factors have been reported elsewhere [18]. The mechanism of pain, previous pain treatments, substance use history [19], and psychosocial history [20-22] should all be considered when making treatment recommendations.

1. Assessment

Pain assessment in last days of life can be challenging as patients become delirious or unresponsive and present with grimacing and moaning only. For patients able to self-report pain, patient reported outcome measures, such as the Edmonton Symptom Assessment System (ESAS), is used for assessment of pain intensity and associated symptoms [17,23]. Personalized Pain Goal may be utilized to identify an individualized pain treatment target and tailor the management plan [24-26]. Patients who are unable to self-report pain may be at greater risk for under-recognition and undertreatment of pain [14,27]. For these individuals, clinicians often rely on their facial and/or body expressions and caregiver input to titrate pain interventions, leaning on the side of caution to ensure patient is not perceived to be suffering.

2. Non-pharmacological management

Non-invasive approaches that may alleviate pain include psychotherapy (e.g., exploring legacy work), relaxation and distraction techniques, music therapy, aromatherapy, and repositioning. Data supporting benefits of these techniques is limited to case reports and preliminary studies [28]. Acupuncture has been found to be helpful for patients with cancer pain and months or years of life expectancy [29,30], although its benefit at the EOL has not been well studied [31,32].

3. Pharmacological management

Opioids are the mainstay of cancer pain management [33-36]. Patients who are opioid-naïve would require low initial dosing with rapid, short acting opioids [33-36]. During the last days of life, there are challenges with medication administration as patients may not be able to swallow. Hence, parenteral, i.e., intravenous or subcutaneous route is preferred/superior in the in-patient setting. Short-acting oral or sublingual opioids are often used in the hospice setting. Data on bioavailability and efficacy of opioids via these routes in last days of life is lacking. Rectal route may be utilized if appropriate [37-40]. Morphine is the most utilized opioid; head-to-head comparison of different opioids have not found a significant difference in analgesic efficacy; however, these studies were not conducted in patients in the last days of life. In general, morphine is the most commonly used parenteral opioid; fentanyl is preferred in patients with renal or hepatic failure; methadone has NMDA antagonist properties and may be particularly useful for neuropathic pain; although the evidence is still evolving and QT prolongation is a concern.

Cognition should be routinely assessed to monitor for opioid-induced neurotoxicity, which is a spectrum of symptoms that include myoclonus, excessive sedation, and delirium [41-43]. Re-evaluation of response to therapy should be conducted at regular intervals with dose adjustment/titration of opioid doses based on 24-hour opioid usage [14]. Dose reduction may be necessary if there are toxicities and side effects, such as over-sedation and intractable nausea. Opioid rotation (switching from one opioid to another) is performed for patients with inadequate pain control despite multiple titrations and in patients who develop opioid-induced neurotoxicity [14,44,45]. In addition, some patients may become increasingly sedated as they enter the dying process, and the dose of opioids may be reduced.

Glucocorticoids may be considered in selected patients as adjuvant to opioids for short term relief of pain in last days of life [46]. Other adjuvant medications such as ketamine (an NMDA receptor antagonist), lidocaine, acetaminophen and nonsteroidal anti-inflammatory drugs may be considered in selected patients, but the evidence in the last days of life is limited and we need to carefully weigh the risks and benefits of these options.

4. Practical tips

Pain management in last days of life in patients with cancer is complex and challenging due to multi-dimensional nature of pain. It should be assessed in form of total pain utilizing a multi-modal approach to address the different dimensions of pain. Opioids remain the mainstay of cancer pain management and can be given via the parenteral (sub-

cutaneously where possible) route. Bioavailability via rectal route is better known than the sublingual (buccal) route, although challenging to administer. Frequent (e.g., every 60 minutes) availability of rescue pain medications in addition to continuous infusion or around the clock dosing, where appropriate, is paramount for optimal pain control.

Delirium

Delirium is an acute fluctuating disturbance in attention, awareness, and cognition, including disorganized thinking, memory impairment, disorientation, or perceptual disturbance [47]. The delirium experience can be highly distressing for patients, caregivers, and healthcare professionals, particularly when positive features (psychomotor agitation, hallucinations) are present [48,49].

In the last days of life, delirium is found in approximately 90% of patients [50] and is a well-established prognostic factor for shortened survival especially in hospitalized and institutionalized patients [50-52]. Despite its high prevalence, delirium is often under-diagnosed and sometimes confused with akathisia, anxiety, insomnia, dementia, depression, or psychosis [53,54]. In patients with cancer, delirium often have multiple causes, such as medications, infections, metabolic abnormalities, and structural abnormalities [49,55]. Only 50% of the delirium episodes have an identifiable cause [48]. For example, simplifying polypharmacy (discontinuing medications such as antibiotics, chemotherapy, antihistamines, ant-cholinergic, sedatives and hypnotics), treatment of infections and correction of fluid and electrolyte imbalance may help to shorten the duration of delirium. Treating the underlying cause is particularly important since no non-pharmacologic or pharmacologic therapies have been found to reverse delirium. However, this should not deter the clinician from looking for and treating any reversible conditions. The diagnosis of terminal delirium is considered if patient is believed to be in the last days to hours of life and the delirium cannot be reversed [56].

1. Assessment

Several screening tools exist to aid in the diagnosis of delirium, including the Confusion Assessment Method (CAM) [57], Delirium Rating Scale (DRS) [58], and Memorial Delirium Assessment Scale (MDAS) [56,59,60]. In our practice, the MDAS is the main tool for assessment and monitoring of delirium. Routine screening, coupled with observations from caregivers and clinicians, help to facilitate the early diagnosis of delirium [61].

2. Non-pharmacologic management

Management of delirium in the last days of life can be challenging. In addition to treatment of potentially reversible causes [62], non-pharmacologic and pharmacologic treatments may be considered [63]. Symptoms of delirium, such as restlessness and hallucinations, can be highly distressing for caregivers and healthcare providers. Family and bedside staff should be educated on diagnosis of delirium, the fluctuating course, and its impact on symptom expression, communication and decision-making capacity.

Non-pharmacologic approaches to management of delirium, such as re-orientation cues, facilitation of physiological sleep patterns and use of hearing or visual aids have been found to be effective for prevention of delirium in many settings [64]; however, few studies have been conducted specifically in the palliative care setting in last days of life. Two controlled studies have been conducted to date to examine the role of non-pharmacologic interventions to prevent delirium in the palliative care setting [65,66]; however, both studies were unable to demonstrate a clear benefit. No studies have specifically tested non-pharmacologic approaches to treat delirium in the palliative care setting. Nevertheless, given that these non-invasive measures are relatively low cost and may help with other conditions (e.g., dehydration), we generally support their use whenever feasible.

3. Pharmacologic management

Patients who experience delirium symptoms, especially agitation and hallucinations, may require pharmacologic interventions. Neuroleptics and benzodiazepines are the mainstays of pharmacological treatment of agitated delirium. Agar et al. [67] conducted a double-blind, randomized controlled trial (RCT) comparing haloperidol and risperidone to placebo, and found that the neuroleptics were associated with worse delirium symptoms and more extrapyramidal side effects. This contrasts with findings from a double-blind RCT by Hui et al. [68] in which patients with hyperactive delirium were assigned to haloperidol and chlorpromazine. Comparison was made between escalation in dose of haloperidol, rotation from haloperidol to chlorpromazine and combination haloperidol and chlorpromazine. Agitation decreased significantly within 30 minutes and remained low at 24 hours in all three groups, suggesting that neuroleptics may be useful for reducing agitation/restlessness in this setting.

Benzodiazepines are reserved for treatment of delirium due to alcohol/benzodiazepine withdrawal, patients with contraindications to neuroleptics or those with refractory agitation despite neuroleptic use [69]. In the single-center, double-blind RCT, Hui et al. [70] examined the use of lorazepam (3 mg) with haloperidol vs. placebo plus haloperidol

alone. They found that the addition of lorazepam to haloperidol resulted in a significantly greater reduction in agitation at 8 hours. Secondary analysis showed that the lorazepam plus haloperidol arm was also associated with increased comfort and required fewer rescue doses [71,72].

Palliative sedation is reserved for highly selected patients with refractory agitated delirium and a short life expectancy of days or less [73-78]. Indications and goals of palliative sedation should be thoroughly discussed among the interdisciplinary team and with caregivers, reinforcing that the goal of palliative sedation is to control symptoms and not to shorten life. This highly specialized intervention should only be conducted in PCUs under supervision of specialized palliative care teams [74,79]. These discussions should be clearly documented in the medical chart. This topic is discussed in further details in an accompanying article in this issue.

4. Practical tips

In practice, we typically try to identify the underlying etiologies of delirium and treat any reversible causes. Non-pharmacologic strategies are implemented where appropriate. Haloperidol is the first-line pharmacologic therapy used for the management of delirium. For patients with predominantly hypoactive features, we usually start with haloperidol 1 mg intravenously every 2 hours as needed for agitation. For patients with agitated delirium, we use haloperidol 1-2 mg intravenously every 4 hours scheduled, and every 2 hours as needed as our first choice. Neuroleptic rotation to chlorpromazine is our second line option [80]. Atypical antipsychotics such as olanzapine, quetiapine and risperidone may also be used as an alternative in some patients [63,67]. However, the use of these medications is limited by their slow onset of action and patients' inability to swallow. Neuroleptic dose escalation and addition of benzodiazepines may also be considered for patients with persistent agitation. Palliative sedation is only considered as a treatment of last resort.

Dyspnea

Dyspnea is a subjective feeling of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity [81]. Dyspnea is multifactorial in patients with cancer, related to progressive cancer (lung metastases, lymphangitic spread, effusions), acute complications (e.g., infections, pulmonary embolism), comorbidities (e.g., chronic obstructive pulmonary disease, heart failure) and others (e.g., cachexia). Psychological factors such as anxiety and depression are significantly correlated with the intensity of

dyspnea perception [82-86]. A National Hospice Study found that 24% of terminally ill patients with cancer had dyspnea in the absence of known cardiopulmonary pathology [87]. Dyspnea is particularly common in the last days of life and typically increases in intensity over time [88,89]. In one study, only 3% of caregivers perceived their loved ones to be breathing comfortably at the end of their lives [90].

1. Assessment

For patients able to self-report their subjective feeling of shortness of breath, patient reported outcome measures, such as ESAS, is used for assessment [17,23]. Dyspnea may also be indirectly measured using surrogate measures or the Respiratory Distress Observation Scale (RDOS) [91,92].

Management of dyspnea requires a multi-disciplinary approach utilizing non-pharmacological and pharmacological measures to avert dyspnea crises in patients with cancer in last days of life [93,94].

2. Non-pharmacological management

A handheld fan directed towards the face can potentially improve breathlessness by stimulation of facial and nasopharyngeal receptors [95-97]. Other measures such as repositioning/posture adjustment and use of walking aids may bring relief [98]. Addressing the psychosocial and spiritual elements of care may also help reduce breathlessness in selected patients. Chest wall vibrations have limited role in last days of life due to the frail nature of these patients.

3. Pharmacological management

Opioid therapy is the drug of choice for alleviating distress related to breathlessness. Multiple RCTs have shown that opioids can relieve dyspnea without compromising the respiratory status [99-102]. However, few studies enrolled patients in the last days of life because of the challenges in conducting research in this population. Parenteral opioids are preferred especially when swallowing becomes difficult. These may be repeated every 30 minutes with close monitoring until patients achieve effective symptom control or in form of a continuous infusion [103].

The role of benzodiazepines is limited to patients with anxiety-associated dyspnea and remains controversial. A recent Cochrane review on the use of benzodiazepines to control breathlessness reported no benefit [104]. Benzodiazepine use was associated with substantial adverse effects, particularly delirium and somnolence. One RCT compared midazolam and morphine in 63 patients with advanced cancer and severe dyspnea (mean score > 8.5 on a scale from 1 to 10) and found that midazolam was superior to morphine in controlling both baseline and breakthrough dyspnea [105]. The most common adverse event was mild somnolence that

did not interfere with function and not different in both groups. However, this study was conducted in patients who were more functional and may not be generalized to patients in the last days of life.

Systemic corticosteroids may be considered as adjuvant in selected patients with structural changes such as central airway narrowing/obstruction and lymphangitic carcinomatosis [46,106]. Bronchodilators may also be considered for patients with evidence of obstructive lung disease. Intravenous diuretics can be helpful in patients with heart failure and lymphangitic carcinomatosis by decreasing lung congestion [98]. The therapeutic role of nebulized diuretics and nebulized opioids for relieving breathlessness remains controversial [99,102,107].

Only few trials have examined the role of oxygen supplementation in patients with cancer in the last days of life. In patients who are hypoxemic, low flow supplemental oxygen, non-invasive ventilation (NIV), or high flow nasal therapy may be considered if consistent with goals of care. High flow nasal cannula has been postulated to improve dyspnea via multiple mechanisms, such as nasopharyngeal washout, augmenting positive airway pressure, gas re-conditioning, and stimulation of cranial nerves. Preliminary studies have found that high flow oxygen may be useful for dyspnea even in patients without hypoxemia [106]; however, this remains investigational and further studies are required. In a recent double-blind, 4×4 crossover trial, Hui et al. [108] reported that high flow oxygen and high flow air provided a rapid and clinically significant reduction of dyspnea at rest in hospitalized non-hypoxemic patients with cancer.

Palliative sedation is reserved for patients with severe refractory dyspnea [73-78].

4. Practical tips

The management of dyspnea is based on goals of care, overall patient prognosis and patient/caregiver preferences. Treatment of underlying causes (e.g., infections) may or may not be feasible. Bedside Management of pneumothorax and malignant pleural effusion with palliative intent can assist with symptom relief in last days of life, however, management is limited by the invasive nature of these procedures and is based on goals of comfort measures. While utilizing the non-pharmacologic modalities, we initiate parenteral opioids as first line for symptomatic management of dyspnea. This is mostly in form of a continuous opioid infusion with as needed nursing bolus every 1 hour offered for relief of shortness of breath. Hypoxemic patients may benefit from trial of supplemental oxygen.

The role of benzodiazepines is limited to patients with anxiety with much caution as concurrent use with opioids is associated with higher risk of respiratory depression. Sys-

temic steroids and bronchodilators assist as adjuvants for short term relief. Role of diuretics is limited to cardiac causes of dyspnea. The use of NIV in dyspneic patients in last days of life remains controversial. Refractory situations may require Palliative sedation.

Bronchial (Hyper) Secretions

Bronchial hypersecretions, also referred to as terminal airway secretions or 'death rattle', occur in 12%-92% [109] of patients. These occur from pooling of upper airway secretions in the throat during the dying process, due to loss of ability to swallow, which creates a noise that is referred to as a "death rattle" [109]. Patients with bronchial hypersecretions generally have a survival of days (median survival 24 hours) [109-111]. Family members and caregivers may perceive these sounds as respiratory distress in the dying person, which may lead to greater distress for the grieving family [112-115].

1. Non-pharmacological management

It is important to educate and reassure caregivers that while the noise can be disturbing for those at bedside, it is not likely to be distressing for the patient. Repositioning of the patient's head to one side may help to move the pooled secretions. Consider discontinuing non-essential parenteral fluids and/or enteral feedings [116]. Gentle, superficial suctioning can be performed especially in patients with head and neck cancers. Deep suctioning should be avoided to prevent trauma and distress.

2. Pharmacological management

Anti-cholinergic medications such as scopolamine (hyoscine) butyl bromide, atropine, and glycopyrrolate are used to reduce secretions [117-119]. In a double-blind RCT, scopolamine (hyoscine) butyl bromide was found to reduce the occurrence of death rattle when given prophylactically [120,121]. However, this medication is not available in the United States. A 2008 small blinded RCT by Likar et al. [122] reported that glycopyrrolate was better than scopolamine (hyoscine) hydrobromide in reducing death rattle. Notable side effects included blurring of vision, potentiation of confusion, excessive drowsiness, restlessness, palpitations, hallucinations, and urinary retention [123].

3. Practical tips

Bronchial hypersecretions can be distressing for caregivers at bedside in the last days to hours of life. Caregivers should be educated and reassured that this phenomenon is a part of the natural process of dying and unlikely to

cause distress to patient. Nonpharmacological interventions include repositioning of the face, reducing excessive fluids and gentle oral suctioning. At our center, glycopyrrolate 0.1 to 0.2 mg subcutaneously or intravenously every 4 hours as needed is often prescribed [124,125].

Seizures

First-time seizures may occur in some patients in the last days to hours of life secondary to new seizure foci from brain metastases or other acute neurologic injuries. Other patients may have recurrent seizures in the last days due to their inability to take oral antiepileptic medications or worsening neurologic complications [126]. Patients may also develop seizures related to opioid-induced neurotoxicity, particularly in the context of acute kidney injury [43,127]. Certain opioids, such as tramadol, meperidine, fentanyl may also lower seizure threshold. Understandably, seizures can be extremely distressing not only for the patients but also family members and care providers.

1. Non-pharmacologic management

As a preventative measure, fall precautions should be put in place for patients with known seizure disorder and/or intracranial space occupying lesions (metastasis, hemorrhage). Patients on opioids should be carefully monitored for early signs of opioid-induced neurotoxicity.

2. Pharmacologic management

For patients with known seizure disorder, we recommend continuing their routine anticonvulsant medications, with transition to non-oral (rectal or parenteral) routes when swallowing is compromised.

For immediate relief, intravenous benzodiazepines are used to control seizures [128,129]. Subcutaneous (lorazepam)

and rectal (diazepam and phenobarbital) routes are limited due to slower onset of action [130] and availability of medication formulations. Intranasal midazolam is the fastest acting benzodiazepine available to control intractable and distressing symptoms and may be used for rapid control of seizures [131]. If necessary, intranasal midazolam may be easily administered by the family at bedside.

3. Practical tips

Intractable seizures may occur as a new symptom in last days to hours of life. Educating caregivers ahead of time is essential. Given the unpredictability of seizures, we always provide an order for intravenous lorazepam 2 mg for 1 dose as needed for seizures, with instructions for nurse to promptly inform the palliative care specialist for further management. Other routes such as subcutaneous route, rectal and intranasal may be considered based on the setting and local availability. Palliative sedation is reserved for refractory seizures in patients with days or less of survival.

Author Contributions

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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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