

Management of dyspnea in advanced cancer patients

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Summary

Dyspnea is a common, disabling symptom of advanced cancer causing distress for patients and families. Breathlessness is a subjective experience and the gold standard of diagnosis is patient self-report. Optimal management involves pharmacological treatment and non-pharmacological interventions. Despite the common occurrence, there are very few controlled studies of the pharmacological management of dyspnea all of them

including only small numbers of patients. Opioids relieve dyspnea and are indicated as first-line treatment in dyspnea of advanced disease of any cause. Benzodiazepines are helpful adjuvant medications. Oxygen is not really indicated unless patients report that it improves their dyspnea. In cases for which symptomatic treatment does not control dyspnea to the patient's comfort, sedation is an effective, ethical option.

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Introduction

Dyspnea is a very common symptom in patients with advanced cancer, with and without direct lung involvement. It is a very distressing symptom to experience and also to witness for the family and the caregivers.

Dyspnea is often defined as an uncomfortable sensation or awareness of breathing.¹⁻³ In 1998, the *American Thoracic Society* consensus statement proposed the following, broader definition: "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses".⁴

Similar to pain, dyspnea is a subjective symptom so patients are the only ones who know whether they are short of breath or not.⁵ Objective measures such as respiratory rate, oxygen saturation, and arterial blood gas measurements frequently do not correlate with the subjective experience of dyspnea.

Incidence

The reported frequency in cancer patients varies

from 21% to 90%, depending on the stage of cancer with an increased prevalence during the last weeks of life.^{1,3} In a large study based on the perceptions by family members, almost 70% of conscious patients who died with lung cancer or multiple organ system failure with a malignant condition had severe dyspnea 3 days prior to death.⁶ Breathlessness is also very frequent (82.1%), at the end of life in children with cancer.⁷

Physiopathology

The control of respiration integrates a variety of afferent activity including that of mechanoreceptors in respiratory muscles, various sensory receptors in the lungs and airways; and chemoreceptors in the carotid bodies and on the ventral surface of the medulla.⁸ All these signals are processed in the bulbopontine region of the brain coordinating the diaphragm with intercostal and accessory muscles to generate the respiratory rhythm.⁹ The pathophysiology of dyspnea remains poorly understood. Despite common belief, hypoxaemia seems to have a less significant role than hypercapnia in dyspnea.³ In clinical practice, it is interesting and important to know that blowing cool air on the face reduces the

Figure 1. Causes of dyspnea divided into direct or indirect tumor effects and treatment-related factors or factors unrelated to cancer.

Directly related to cancer	Related to cancer therapy
Primary/metastatic parenchymal lung involvement Airway obstruction (intrinsic or extrinsic tumor) Carcinomatous lymphangitis Pleural tumor Malignant pleural effusion Pericardial effusion Superior vena cava syndrome Tumor microemboli Phrenic nerve paralysis Atelectasis Tracheal-oesophageal fistula Chest-wall invasion (carcinoma en cuirasse) Pathological chest-wall fractures	Surgery (after lobectomy or pneumonectomy) Radiation pneumonitis Chemotherapy-induced pulmonary fibrosis Chemotherapy-induced cardiomyopathy
Indirectly related to cancer	Unrelated to cancer
Pneumonia Cachexia Anaemia Electrolyte abnormalities Pulmonary embolus Paraneoplastic syndromes	Chronic obstructive pulmonary disease Asthma Congestive heart failure Cardiac ischaemia Arrhythmias Pulmonary vascular disease Obesity Neuromuscular disorders Aspiration Anxiety Pneumothorax Interstitial lung disease Psychosocial/spiritual pain

sensation of breathlessness by stimulating receptors in the trigeminal nerve located in the cheek and nasopharynx.¹⁰ This explains how open windows and air movement, such as a fan, can be very helpful.⁴ The causes of dyspnea are often multifactorial in advanced cancer and can be classified in direct or indirect tumor effects, treatment-related factors or factors unrelated to cancer (*Figure 1*).³

Management of Dyspneic Palliative Patients

Etiologic treatments must be considered when possible and symptomatic treatments are indicated only when specific approaches do not relieve the patient or if they are not appropriate. The therapeutic goal of symptomatic management is to relieve the patient's sense of the effort of breathing, involving both non-pharmacological and drug-based management.³ It is essential to explain the cause of dyspnea and the treatment plan to both patients and their families.⁵

Pharmacological Interventions

Most clinical experience relates to the use of opioids, oxygen, corticosteroids and benzodiazepines but there are few (and only small) controlled studies of the pharmacological management of breathlessness.^{11,12}

Opioids

Not so long ago, the use of opioids in the management of dyspnea was feared by clinicians who worried about causing respiratory depression.¹¹ In 1990, *Bruera et al* were the first to study the potential of opioids in controlling dyspnea in cancer patient. In a placebo-controlled crossover study, they demonstrated that opioids relieved dyspnea without evidence of respiratory depression and without change in respiratory rate or oxygen saturation.¹³

The mechanism by which opioids relieve dyspnea is not completely understood. Opioids seem to have a multitarget effect by reducing anxiety and sensi-

Key messages for clinical practice

1. Dyspnea is a common symptom in advanced cancer which is very distressing for patients and their families, and should be managed actively.
2. Opioids relieve dyspnea and are indicated as first-line treatment in dyspnea of advanced disease of any cause.
3. Oxygen is not always necessary and only indicated if it makes the patient feel more comfortable.
4. Do not be caught off-guard by predictable problems in case of dyspnea crisis (written respiratory distress protocol).
5. Death Rattle : Anticipate and avoid (hyper)hydratation.
6. Spend time communicating with patients and their family.

vity to hypercapnea and by improving cardiac function (preload reduction).¹⁴

A systematic review of the use of opioids in the management of dyspnea including 18 double-blind, randomized, placebo-controlled trials of opioids for dyspnea from any disease, shows a statistically significant positive effect of oral and parenteral opioids on the sensation of breathlessness.¹⁵ However, concerning nebulised opioids, the results suggest that they are no better than nebulised normal saline.¹⁵ The opioid dose should be individualized and titrated until the patient states that he is comfortable and in the case of non-verbal/confused patients until restlessness, agitation or apparent breathlessness are controlled.¹⁴⁻¹⁶ It is important to distinguish patients who have not been taking opioids regularly (opioid naïve patient) and patients who are already taking opioids regularly for pain or dyspnea.⁵ In patients already taking opioids, the baseline dose can be increased by 25% to 50% depending on the severity of the dyspnea.¹⁶

As for pain treatment, opioid side-effects such as constipation and nausea, should be prevented by prophylactic anti-emetic and stimulant laxative.¹⁴

Oxygen

Oxygen is often prescribed for the palliation of breathlessness but its use remains controversial.¹¹ Evidence from randomized controlled trials suggests that both oxygen and air can reduce dyspnea in patients with cancer.¹⁷ It seems that it is not the correc-

tion of hypoxemia that is important, but rather the flow of gas.^{9,18} There is undoubtedly a subgroup of patients who obtain substantial benefit from oxygen (or air inhalation) but there are little data enabling clinicians to predict which patients will benefit.^{17,18}

Corticosteroids

Corticosteroids are indicated in the presence of bronchial obstruction, superior vena cava syndrome or lymphangitic carcinomatosis but there are no controlled trials supporting this.¹² As steroids may cause myopathy which can involve the respiratory muscles and can be very debilitating, these medications should be used cautiously.⁴ If the cause of breathlessness is unclear, a brief trial of oral dexamethasone (8-12 mg/d) can be considered. However, if there is no improvement after 4 days, the treatment should be stopped.¹¹

Benzodiazepines

Dyspnea can lead to anxiety, and anxiety can exacerbate dyspnea.³ Anxiolytics are frequently prescribed for patients with dyspnea. In the absence of meta-analyses or randomized controlled trials of the use of benzodiazepines in cancer dyspnea, the evidence for their effectiveness is not established and benzodiazepines alone should not be considered first-line therapy for dyspnea.^{9,12} However, treatment of anxiety does have a role in a subset of patients for whom it is a prominent component of the distress.³ In urgent situations, short-acting benzodiazepines

Figure 2. Example of a dyspnea distress protocol.

1 site (SC) : MIDAZOLAM (Dormicum)	
< 70kg 5mg BZD (-)	> 70 kg 20mg BZD (+)
1 other site (SC) : MORPHINE : 10 mg - 50 mg maximum (50 % dose in 4 hours) SCOPOLAMINE 0,5 à 0,75 mg In the same syringe	

can be used. In this setting, midazolam not only offers a short half-life without active metabolites but also an excellent subcutaneous bioavailability.¹⁹ Moreover, midazolam induces more sedation than any other benzodiazepine.

Nonpharmacological Interventions

In addition to pharmacologic interventions, some general strategies for reducing dyspnea are positioning (patients may benefit from sitting upright in bed or a chair), scheduling activities, keeping the room cool and having a fan blowing gently on the patient.⁵ A very recent review including randomized-controlled and controlled clinical trials assessing the effects of non-pharmacological and non-invasive interventions to relieve breathlessness in advanced stages of disease concludes that breathing training, neuro-electrical muscle stimulation and chest wall vibration appear to be effective non-pharmacological interventions for relieving breathlessness.²⁰

Acute severe dyspnea

Diagnosis of acute severe dyspnea occurring during the last hours of life requires crisis intervention. Reassurance and having a management plan for severe dyspnea can reduce the fear of dying (*Figure 2*).⁵ Respiratory distress should be managed aggressively with parenteral opioids and sedatives so that patients are breathing comfortably and are moderately sedated.^{5,9} Sedation is an effective, ethical option in order to optimally manage severe dyspnea and it should be discussed with the patient, his family and the caregiver team (written prescription).³

Death Rattle

Death rattle is a frequent symptom in the last hours of life and it may be very disturbing to family and

caregivers.²¹ A biodynamic analysis shows that inappropriate fluid intake may exaggerate a relative fluid excess and may induce or increase terminal pulmonary rattles. It is therefore advisable to be cautious about oral or i.v. fluid administration in order to avoid adding to the discomfort of the last moments of life.²² Scopolamine can reduce secretions and has also a sedative effect.²¹

Conclusion

Dyspnea is a common symptom in advanced cancer which is distressing for patients and their families, and should be managed actively. Explaining the cause of dyspnea and the treatment plan to both patients and their families is essential. Despite the common occurrence, there are few and only small controlled studies of the pharmacological management of breathlessness. Opioids relieve dyspnea and are indicated as first-line therapy for the management of dyspnea. Oxygen is only indicated if patients say that it makes them feel better. Benzodiazepines can also be useful but should never be used alone. Keeping the room cool and placing a fan with the air blowing in the direction of the patient's face are efficacious non-pharmacological measures. There is a definite need for further research and additional randomized controlled trials to supplement the limited evidence base currently available.

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