

Treatment of dyspnoea in advanced cancer patients: ESMO Clinical Practice Guidelines[†]

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introduction

Dyspnoea is a frequent symptom in advanced cancer patients with the highest prevalence in lung cancer (up to 74%) increasing in the terminal phase (up to 80%) with major impact on the quality of life of the patient, his or her family, as well as the caregivers [1–5]. Patients describe dyspnoea as suffocating, choking or tightness of breath. Qualitative data have shown that the symptom can be described along three dimensions:

- air hunger—the need to breathe while being unable to increase ventilation;
- effort of breathing—physical tiredness associated with breathing;
- chest tightness—the feeling of constriction and inability to breathe in and out.

In summary, it can be defined as subjective perceived breathlessness, difficult breathing or shortness of breath. The experience of dyspnoea encompasses physical, as well as psychological, social and spiritual domains [6–8]. Recently, the term ‘total dyspnoea’ has been proposed to capture the complexity of the symptom [9, 10]. Moreover, dyspnoea has been demonstrated to be one of the most distressing symptoms in cancer patients [11]. This suggests a multidisciplinary approach focusing on the patient’s psychological, social and spiritual needs, as well as on the physical symptoms [12–14].

assessment

Breathing discomfort varies in intensity that may not be associated with hypoxaemia, tachy-(increased respiratory rate), brady-(reduced respiratory rate) or orthopnoea (normal respiratory rate). Since dyspnoea is completely subjective in perception, the most valid assessment instrument is the patient-reported outcome addressing the multidimensional and multifactorial nature of the symptom [15–19]. If this is impossible due to impaired communicative capability of the patient, relative or caregiver, reported dyspnoea may be helpful (Table 1).

The differentiation between continuous, episodic, breakthrough or crisis breathlessness, as well as the evaluation of onset, exacerbating and relieving factors is important in order to

adjust the therapy appropriately, taking into consideration disease-modifying, causative and symptomatic treatment options [20]. Dyspnoea often leads to severe anxiety but severe anxiety can cause dyspnoea as well [19, 21–23]. Therefore, the psychosocial dimension and environmental conditions should not be omitted and very often play a major role in the clinical condition.

management strategies

treating reversible causes

With regard to the patient’s general condition and the state of disease, causative therapeutic options should be considered and discussed with the patient before starting symptomatic treatment, except in the case of emergency (acute suffocation). The required physical and technical examinations (complete blood count, electrolytes, creatinine, oximetry and full blood gas assessment, electrocardiogram, brain natriuretic peptide or chest X-ray and computed tomography scan) must correspond to the patient’s performance status as well as to the putative resulting therapeutic options [24] (Table 2).

non-pharmacological interventions

Little evidence but sufficient clinical consensus is available concerning non-pharmacological interventions. They should be offered before starting pharmacological interventions and should accompany them afterwards [26, 27].

They include education of the patient, and his or her relatives, about simple measures for ameliorating the symptom, such as cooling the face, opening windows, using small ventilators, adequate positioning (e.g. coachman’s seat, elevation of the upper part of the body), respiratory training, the use of a walking frame or a walker [28–30].

It is very important that the patient and the caregivers are familiar with these treatment options and can use them whenever they want [31]. This contributes to the reduction of helplessness and anxiety. In addition to technical support, psychological training (relaxation) contributes to the prevention of developing a panic attack when breathlessness is experienced, by improving emotional control during breakthrough dyspnoea [32].

oxygen. There is no evidence that oxygen therapy relieves dyspnoea, unless the patient suffers from hypoxaemia [33–37]. Considering its disadvantages (being an invasive intervention

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Table 1. Dimensions of dyspnoea

Dimension	Criterion	Measurement
Sensory-perceptual experience	Intensity	NRS, VAS
Affective distress	Emotional unpleasantness	NRS, VAS, HADS
Impact on daily life	Meaning for social contact, functioning, quality of life	CRQ, EORTC-QLQ-C15-PAL, MRC, SF12

NRS, Numerical Rating Scale; VAS, visual Analogue Scale; MRC, Medical Research Council; CRQ, Chronic Respiratory Disease Questionnaire; HADS, Hospital Depression and Anxiety scale; SF12 Health survey; EORTC-QLQ-C15-PAL questionnaire to assess the quality of life of palliative cancer care patients.

Table 2. Pathophysiology and causative intervention (examples only) [25]

Pathophysiology	Targeted intervention
Pleural effusion	Pleural drainage, pleurodesis
Cancer-induced airways obstruction	Endoscopic or surgical intervention (stent, laser, argon-beamer) Localised radiotherapy
Anaemia	Transfusions Erythropoietin administration for chemotherapy-induced anaemia
Infections, e.g. pneumonia	Antibiotics, antifungal drugs
Airway obstruction and chronic obstructive pulmonary disease as comorbidity	Airway dilators, corticosteroids
Haemoptysis	Antifibrinolytics, endoscopic or surgical intervention (stent, laser, argon-beamer), irradiation
Pulmonary congestion	Diuretics or other appropriate intervention
Pericardial effusion	Pericardial puncture, pericardiodesis
Upper venous congestion	Corticosteroids, irradiation, stenting of the vena cava, anticoagulation
Chest pain	Optimised analgesia

requiring tubing and tanks), its risk of nosebleeds from the nasal cannula, and the patient's psychological addiction to this 'umbilical cord', it cannot be recommended for routine use. Even in the home-care setting, it serves as a surrogate for caregivers who may feel helpless and distressed when watching a breathless family member at home. Oxygen could be used for a short period before physical efforts or eating.

Oxygen supplementation through ventouri masks can offer significant alleviation of dyspnoea in patients with hypoxaemia, if the patient suffered from chronic obstructive pulmonary disease as a co-morbidity and has been on oxygen before.

pharmacological treatment

opioids. Opioids are the only pharmacological agents with sufficient evidence in the palliation of dyspnoea [38–41]. They can be used in opioid-naïve as well as in opioid-tolerant patients without causing relevant breath depression or impaired oxygenation or increase in CO₂ concentration [42]. Nevertheless, patients receiving opioids for breathlessness experience the well-known opioid-related unwanted side effects, e.g. initial nausea and persistent constipation. The mechanism of the antidyspnoeic effect of opioids seems complex and is mediated via opioid receptors of the cardio-respiratory system as well as different areas in the central nervous system [43–49]. There is

some evidence for a close relationship between dyspnoea and anxiety. Opioids reduce the unpleasantness of dyspnoea. Although evidence has been provided only for oral and parenteral morphine, diamorphine and dihydrocodeine, larger series, retrospective studies and case reports suggest that no opioid is superior to another and that hydromorphone, fentanyl and oxycodone may also be used [46, 50–52]. Morphine should be avoided in patients with severe renal insufficiency, while dosage and dosage intervals should be adapted to the renal function for all μ -opioids because of their renal elimination [53–55].

Normal-release preparations of oral/rectal opioids may be used for titration, switching to sustained preparation afterwards [56]. Subcutaneously and intravenously applied opioids are effective, with the intravenous form having the most rapid onset. There is no evidence for the efficacy of nebulised or inhaled opioids [18, 57, 58]. The importance of buccal, nasal or transdermal preparations still remains unclear.

In opioid-naïve patients, the starting dose for dyspnoea is smaller than that for pain palliation [59]. On the contrary, patients receiving opioids for analgesia require an increase of dosage up to 25% or 50% [60] (Table 3).

benzodiazepines. Benzodiazepines can be used in cases of non- or insufficient response to opioids, either alone or in addition to

Table 3. Starting doses of opioids for the palliation of dyspnoea

Opioid	Starting dose opioid naive	Starting dose in concomitant opioid intake
Morphine	2.5–5 mg/4 h p.o. 1–2.5 mg/4 h s.c.	Regular opioid dose + 1/6 of the daily opioid intake
Hydromorphone	1.3 mg/4 h p.o. 0.2–0.5 mg/4 h s.c.	Regular opioid dose + 1/6 of the daily opioid intake

p.o., oral; s.c., subcutaneous.

Table 4. Recommended dosages of benzodiazepines for the palliation of dyspnoea

Benzodiazepine	Dosage
Lorazepam	0.5–1.0 mg/6–8 h p.o. or s.l.
Midazolam	2.5–5 mg/4 h s.c. 10–30 mg/24 h s.c.

s.c., subcutaneous; s.l., sublingual; p.o. oral.

opioids, especially in patients experiencing anxiety [61–65]. They predominantly reduce the unpleasantness of dyspnoea and also act as anxiolytics. Therefore, their use can be recommended, especially in the far advanced stages and in the dying patient. Lorazepam and midazolam seem to be the most commonly used substances. Nevertheless, the impact of muscle relaxation and its potential contribution to the intensification of dyspnoea, especially in cancer cachexia and sarcopenia, should be taken into consideration (Table 4).

other drugs. ‘Neuroleptics’ such as phenothiazines act as anxiolytics and sedatives. This led to the assumption that they may be helpful in treating dyspnoea. To date, proven evidence is lacking and therefore they cannot be recommended [66–68].

‘Antidepressants and buspirone’ are reputed to exert some antidyspnoeic efficacy as mood-enhancing medication; nevertheless, this has not yet been proven [69–78].

‘Steroids’ proved to be effective in dyspnoea caused by lymphangiosis carcinomatosa, radiation pneumonitis, superior vena cava syndrome, an inflammatory component, or in (cancer-induced) obstruction of the airways [79–83]. They should not be used routinely other than for these indications [1, 84–86].

dyspnoea in the dying patient

Dyspnoea is a frequent and perhaps one of the most distressing symptoms in the last days of life [87]. The basis of coping with this suffering is the same as that described within the palliative context. Nevertheless, the focus of treatment shifts to pharmacological treatment (including terminal sedation with benzodiazepine in addition to opioids) if treatment is insufficient [88–92]. Human attendance and empathy are paramount.

Death rattle sometimes aggravates the burden of relatives. Therefore, the clarification of its nature is paramount for them. Pharmacological interventions include reduction of artificial

hydration, adding antisecretory drugs such as atropine, hyoscine or glycopyrronium bromide and optimise positioning of the dying.

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development. They are based on the international literature and the available scientific guidelines and the relevant literature has been selected by the expert authors. Because these recommendations are not based on a systematic review of the evidence, undertaken by guideline development group members, with support from the SIGN Executive, they are not graded. For this purpose, we refer to the scientific German S3 guidelines. However, this manuscript has been subjected to an anonymous peer review process.

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These clinical recommendations refer to the German scientific stage 3 guideline ‘Palliative Care’, part of the guideline initiative covering the whole area of oncology. The guideline ‘Palliative Care’ has been masterminded by members of the German Society for Palliative Care, the German Cancer Society and the German Cancer Aid in collaboration with many other scientific societies. It has been promoted by the Association of the Scientific Medical Societies in Germany (AWMF) and published in May 2015 (http://www.awmf.org/uploads/tx_szleitlinien/128-001OLI_S3_Palliativmedizin_2015-04.pdf).

conflict of interest

MK has been investigator of the Effendys Study sponsored by TEVA Pharmaceutical Industries and is member of the advisory board of this company. NC has declared no potential conflicts of interest.

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