Evaluation of Diagnostic and Treatment Approaches to Acute Dyspnea in a Palliative Care Setting Among Medical Doctors with Different Educational Levels

Klaus Hackner  
Karl Landsteiner University of Health Sciences: Karl Landsteiner Privatuniversitat fur Gesundheitswissenschaften  
https://orcid.org/0000-0002-6378-5840

Magdalena Heim  
Karl Landsteiner University of Health Sciences: Karl Landsteiner Privatuniversitat fur Gesundheitswissenschaften GmbH

Eva Katharina Masel  
Medical University of Vienna: Medizinische Universitat Wien

Gunther Riedl  
Landesklinikum Thermenregion Baden: Landesklinikum Baden

Michael Weber  
Karl Landsteiner University of Health Sciences: Karl Landsteiner Privatuniversitat fur Gesundheitswissenschaften GmbH

Matthäus Strieder  
Karl Landsteiner University of Health Sciences: Karl Landsteiner Privatuniversitat fur Gesundheitswissenschaften GmbH

Sandra Danninger  
Medical University of Vienna: Medizinische Universitat Wien

Martin Pecherstorfer  
Karl Landsteiner University of Health Sciences: Karl Landsteiner Privatuniversitat fur Gesundheitswissenschaften

Gudrun Kreye  
gudrun.kreye@krems.lknoe.at  
Karl Landsteiner University of Health Sciences: Karl Landsteiner Privatuniversitat fur Gesundheitswissenschaften GmbH

Research Article

Keywords: palliative care, cancer, medical doctors, dyspnea, case report

Posted Date: December 2nd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-986858/v1
Abstract

Background

Dyspnea is common in patients with advanced cancer. Diagnostic procedures in patients with dyspnea are mandatory but often time-consuming and hamper rapid treatment of the underlying refractory symptoms. Opioids are the first-line drugs for the treatment of refractory dyspnea in palliative care patients with advanced lung cancer.

Methods

To evaluate the knowledge levels of medical doctors with different educational levels on the diagnosis of and treatment options for dyspnea in patients with advanced lung cancer in a palliative care setting, a case report and survey was distributed to physicians at the University Hospital Krems, describing acute dyspnea in a 64-year-old stage IV lung cancer patient. A total of 18 diagnostic and 22 therapeutic options were included in the survey. The physicians were asked to suggest and rank in order of preference their diagnosis and treatment options. Statistical analyses of the data were performed, including comparison of the responses of the senior doctors and the physicians in training.

Results

A total of 106 surveys were completed. The respondents were 82 senior physicians and 24 physicians in training (response rates of 86% and 80%, respectively). Regarding diagnostic investigations, inspection and reading the patient’s chart were the most important diagnostic tools chosen by the respondents. The choices of performing blood gas analysis (p=0.01) and measurement of oxygen saturation (p=0.048) revealed a significant difference between the groups, both investigations performed more frequently by the physicians in training. As for non-pharmacological treatment options, providing psychological support was one of the most relevant options selected. A significant difference was seen in choosing the option of improving a patient’s position in relation to level of training (65.9% senior physicians vs. 30.4% physicians in training, p=0.04). Regarding pharmacological treatment options, oxygen application was the most chosen approach. The second most frequent drug chosen was a ß-2 agonist. Only 9.8% of the senior physicians and 8.7% of the physicians in training suggested oral opioids as a treatment option, whereas intravenous opioids were suggested by 43.9% of the senior physicians and 21.7% of the physicians in training (p=0.089). For subcutaneous application of opioids, the percentage of usage was significantly higher for the physicians in training than for the senior physicians (78.3% vs. 48.8%, p=0.017, respectively).

Conclusion

The gold standard treatment for treating refractory dyspnea in patients with advanced lung cancer is opioids. Nevertheless, this pharmacological treatment option was not ranked as the most important. Discussing hypothetical cases of patients with advanced lung cancer and refractory dyspnea with
experienced doctors as well as doctors at the beginning of their training may help improve symptom control for these patients.

**Introduction**

Dyspnea is one of the most common symptoms in patients with advanced cancer. In patients with heterogeneous cancer entities, the reported prevalence of dyspnea ranges from 19–64% [1, 2]. However, in the last weeks of life, the prevalence of dyspnea increases from 49–64% [3, 4].

First-line treatment with opioids is the gold standard for managing dyspnea in patients with advanced cancer [5–9]. However, respiratory depression remains a major concern for many physicians, which may lead to reluctance to use opioids in these patients.

**Diagnostic procedures for dyspnea**

For optimal treatment of dyspnea, the underlying cause of the condition must be identified. Therefore, selected diagnostic procedures are necessary (Figure 1) [10]. First, a comprehensive clinical investigation and assessment of the patient is mandatory, including inspection, auscultation, and percussion [11]. After clinical assessment, the patient might immediately benefit from adequate purposive treatment. Further investigations include evaluation of the medical history and the current problem, capturing the main facts from the patient’s chart, and, when indicated, chest x-ray, measuring oxygen saturation, and assessing the hemoglobin level [10]. In cases of acute dyspnea, assessing the patient’s medical history verbally might be difficult; instead, the patient’s chart should be used to gain essential information.

Physical examination should include a quick assessment of the patient’s general condition, which may reveal obvious signs of infection, hypoxia, anemia, bronchospasm, or effusions. This may require further second- and third-line investigations. Before performing these investigations, treatment should be initiated to alleviate the patient’s symptoms as soon as possible (Figure 1) [10].

**Treatment of dyspnea**

The primary goal of treating breathless cancer patients is symptom alleviation. Some non-pharmacologic strategies may be beneficial in the management of acute dyspnea [12, 13]. A simple method is to help the patient sit upright in a bed or chair, or in front of an open window or a fan [14, 15].

Oral or parenteral opioids are the drugs of choice as the first-line treatment in the pharmacological management of refractory dyspnea [5, 8, 16]. Many studies have shown the value of opioids for dyspnea in terminal patients with malignancy [7]. Opioids can relieve dyspnea by depressing the respiratory drive and changing the patient’s perception of dyspnea [17].

Currently, no evidence of a consistent beneficial effect of benzodiazepines, phenothiazines, antidepressants, diuretics, or oxygen as first-line treatments exists. Benzodiazepines appear not to reduce dyspnea directly, but they seem to decrease anxiety and can therefore be used in combination with other
drugs [16, 18]. Corticosteroids, bronchodilators, methylxanthines, diuretics, and other drugs are used as second- or third-line drugs [19–23]. Oxygen therapy is still considered controversial in the management of dyspnea, as few data support its use in non-hypoxic patients [24]. In practice, supplemental oxygen can be considered in patients with an oxygen saturation of less than 90% [25, 26].

The aim of this study was to evaluate medical doctors’ (MDs) attitudes toward diagnostic and treatment approaches in a case report of a patient with Union for International Cancer Control (UICC) stage IV lung cancer and acute dyspnea.

**Material And Methods**

A case report about a UICC stage IV lung cancer patient with massive pulmonary disease progression was distributed to MDs (senior physicians and physicians in training) (see Appendix). The MDs were asked to read the case report and imagine a scenario where they were contacted by a nurse because the patient was suffering from acute worsening of dyspnea. After reading the case report, the MDs were asked to rank their preferred diagnostic procedures and treatment options. To ensure that the MDs understood how to rank the diagnosis and treatment options, a recipe for how to bake a cake was provided as a model for consecutive options that should be ranked. The MDs were asked to read the recipe before ranking their decisions about the case report (see Appendix).

A detailed literature review was used to include all possible diagnostic procedures and treatment options for patients with advanced cancer and dyspnea. In total, 18 diagnostic and 22 treatment options were offered to the participants. The MDs were asked to rank their diagnosis plans by writing numbers next to the 18 options. If the participants did not consider one or more of the given diagnostic options at all, the field next to the option was left blank. The same procedure was performed with the treatment options.

The default first-line investigations included reading the patient's chart, clinical inspection, auscultation, and, optionally, performing a chest x-ray and measuring oxygen saturation. Before continuing with second- or third-line investigations, symptomatic treatment should be started. Optimal pharmacologic treatment for this patient would include oral or parenteral opioids after first-line investigations to immediately alleviate the patient's symptoms. In addition, non-pharmacological interventions, such as placing the patient in an upright position or opening a window, would ameliorate symptoms.

All data were collected at the University Hospital Krems. Part of the introductory phase for physicians in training in this tertiary hospital is a basic medical seminar. This compulsory seminar includes lectures about emergency medicine, ethics, pharmacology, law, the Critical Incident Reporting System (CIRS), and palliative care. The physicians in training received the case report before the lecture on palliative care started and were asked to complete it paper based.

In addition, the questionnaire was distributed to senior physicians at the same medical institution paper based.
For the present study, as no patient data were involved, assessment by and permission from an ethics committee was not required, as confirmed by the local ethics committee of Karl Landsteiner University of Health Sciences.

For the statistical analyses, absolute frequencies and percentages are reported as descriptive statistics. Not all respondents answered each question completely; therefore, the numbers that constituted the basis for the analysis are included in the reported response. To compare two different groups (i.e., senior physicians vs. physicians in training), Fisher's exact test was used, and a Fisher-Halton-Freeman test was used to assess the comparison of three or more groups. These tests deliver reliable results, even with a few observations. Data analysis was performed using the statistical program Microsoft Office Excel (version 15.27) and IBM SPSS Statistics (version 27, Armonk, NY, USA). A p-value $\leq 5\%$ was considered statistically significant. To avoid an increasing error of the second type, no multiplicity corrections were made.

Results

The questionnaire was distributed to 95 senior physicians and 30 physicians in training attending the basic medical seminar. The senior physicians included 38 internal medicine specialists, 12 pneumologists, 15 radiation oncologists, 10 general practitioners, and 20 anesthesiologists (n=95). Eighty-two senior physicians ranked their diagnostic and therapeutic preferences for the case report (response rate 86%). In total, seven senior physicians had a diploma in palliative care. There was no significant difference in the answers of the senior physicians with a diploma in palliative care compared to those without. Of the 30 physicians in training, 24 (response rate 80%) ranked their diagnostic recommendations, while 23 (response rate 76%) indicated their therapeutic preferences concerning this case report.

Diagnostic approaches

Ranking of diagnostic procedures

The senior physicians ranked inspection of the patient first among the diagnostic procedures, as it was chosen as the most important first-line investigation by 24 (29.27%) participants. Measuring oxygen saturation and reading the patient's chart were both ranked first by 19 (23.17%) of the senior physicians, hence constituting the second most important diagnostic procedures (Supplementary Figure 1). For the physicians in training, reading the chart constituted the most important first-line investigation, as it was ranked first by 9 (37.5%) participants. Inspection and taking the patient's history were both ranked first by 5 (20.83%) of the physicians in training, marking the second most important procedures for the physicians in training (Supplementary Figure 2).

Investigation of electrolytes, performing an echocardiogram or a ventilation-perfusion scan, more blood work, a chest x-ray, or evaluation of D-dimer levels were never ranked first, either by the senior physicians
or by the physicians in training. For further results, see *Supplementary Figures 1–2.*

**Frequency of diagnostic procedures**

Significant differences between the senior physicians and the physicians in training were found for auscultation (trend toward significance), blood gas analysis, and measurement of oxygen saturation (Table 1). Auscultation was chosen by 95.1% of the senior physicians, whereas only 83.3% of physicians in training considered this option an important diagnostic tool in this situation (p=0.076). Blood gas analysis was suggested by 61% of the senior physicians and 95.8% of the physicians in training (p=0.001). Measuring oxygen saturation was chosen by 82.9% of the senior physicians and 62.5% of the physicians in training (p=0.048).
Table 1  
Frequency of chosen diagnostic options – Diagnostic option vs. level of training (senior physicians*physicians in training)

| Diagnostic option               | Senior physicians (n=82) | Physicians in training (n=24) | p-value* |
|---------------------------------|--------------------------|------------------------------|----------|
|                                 | n (%)                    | n (%)                        |          |
| No                              | Yes                      | No                           | Yes      |
| Auscultation                    | 4 (4.9)                  | 78 (95.1)                    | 4 (16.7) | 20 (83.3) | 0.076 |
| Bedside spirometry              | 82 (100)                 | 0                            | 24 (100) | 0         | n.a.  |
| Blood gas analysis              | 32 (39.0)                | 50 (61.0)                    | 1 (4.2)  | 23 (95.8) | 0.001 |
| Blood pressure                  | 69 (84.1)                | 13 (15.9)                    | 23 (95.8) | 1 (4.2)  | 0.183 |
| Chest x-ray                     | 51 (62.2)                | 31 (37.8)                    | 10 (41.7) | 14 (58.3) | 0.1   |
| Creatine kinase                 | 61 (74.4)                | 21 (25.6)                    | 20 (83.3) | 4 (16.7)  | 0.426 |
| CT scan                         | 72 (87.8)                | 10 (12.2)                    | 21 (87.5) | 3 (12.5)  | 1.000 |
| D-dimer                         | 61 (74.4)                | 21 (25.6)                    | 16 (66.7) | 8 (33.3)  | 0.448 |
| Dyspnea scale                   | 69 (84.1)                | 13 (15.9)                    | 23 (95.8) | 1 (4.2)  | 0.183 |
| ECG                             | 35 (42.7)                | 47 (57.3)                    | 9 (37.5)  | 15 (62.5) | 0.814 |
| Echocardiogram                  | 75 (91.5)                | 7 (8.5)                      | 24 (100)  | 0         | 0.346 |
| Electrolytes                    | 75 (91.5)                | 7 (8.5)                      | 21 (87.5) | 3 (12.5)  | 0.691 |
| Inspection                      | 22 (26.8)                | 60 (73.2)                    | 8 (33.3)  | 16 (66.7) | 0.608 |
| More blood works                | 76 (92.7)                | 6 (7.3)                      | 19 (79.2) | 5 (20.8)  | 0.120 |
| Oxygen saturation               | 14 (17.1)                | 68 (82.9)                    | 9 (37.5)  | 15 (62.5) | 0.048 |
| Percussion                      | 51 (62.2)                | 31 (37.8)                    | 18 (75.0) | 6 (25.0)  | 0.332 |
| Read chart                      | 23 (28.0)                | 59 (72.0)                    | 4 (16.7)  | 20 (83.3) | 0.301 |
| Taking history                  | 40 (48.8)                | 42 (51.2)                    | 14 (58.3) | 10 (41.7) | 0.489 |
| Ventilation-perfusion scan      | 79 (96.3)                | 3 (3.7)                      | 23 (95.8) | 1 (4.2)  | 1.000 |

*Fisher’s exact test was applied.

ECG: electrocardiogram; n.a.: not applicable.

Other options for diagnostic procedures did not show significant differences between the two groups. Concerning the senior physicians, 73.2% vs. 66.7% of the physicians in training acknowledged inspection as a diagnostic option (p=0.608), while 37.8% of the senior physicians and 25% of the physicians in
training would perform percussion during the physical examination \( (p=0.332) \). Reading the patient's chart was considered by 72\% of the senior physicians and 83.3\% of the physicians in training to be a useful diagnostic option for gaining additional information about the patient's present condition \( (p=0.301) \). For half of the physicians (51.2\% of the senior physicians and 41.7\% of the physicians in training), taking a brief history represented an appropriate option \( (p=0.489) \), while 37.8\% of the senior physicians and 58.3\% of the physicians in training considered a chest x-ray a validated tool for diagnosis \( (p=0.1) \). Measuring the level of the patient's electrolytes was suggested by 8.5\% of the senior physicians and 12.5\% of the physicians in training \( (p=0.691) \). Echocardiography was considered by 8.5\% of the senior physicians and none of the physicians in training \( (p=0.346) \). No participant chose bedside spirometry as a diagnostic option. The distribution of those few participants who considered a computed tomography (CT) scan as a diagnostic option was almost equal: 12.2\% of the senior physicians and 12.5\% of the physicians in training indicated this as a further expedient diagnostic tool \( (p=1.000) \). Low proportions in both groups (3.7\% of the senior physicians and 4.2\% of the physicians in training) chose a ventilation-perfusion scan as an investigation \( (p=1.000) \).

**Therapeutic approaches**

**Ranking of therapeutic options**

Delivery of oxygen was chosen as the most important therapeutic approach by the senior physicians: 43 (52.44\%) ranked this first as a first-line therapy. Improving the patient's position was ranked first by 14 (17.07\%) of the senior physicians, hence constituting the second important therapeutic procedure. The third important therapy ranked first by the senior physicians was providing psychological support, as indicated by 11 (13.41\%) of the senior physicians (Supplementary Figure 3). Among the physicians in training, 12 (50\%) ranked the delivery of oxygen first, and four (16.67\%) ranked the application of subcutaneous opioids first. Three (12.5\%) of the physicians in training suggested providing psychological support first (Supplementary Figure 4). For further results, see Supplementary Figures 3–4.

**Frequency of therapeutic options**

Non-pharmacological treatment options: Providing psychological support to patients with acute dyspnea is one of the most relevant non-pharmacological treatment options, and 73.2\% of the senior physicians and 73.9\% of the physicians in training would choose this tool \( (p=1) \). Improving the patient's position was chosen by more than half of the senior physicians (65.9\%) and only 30.4\% of the physicians in training \( (p=0.004) \). Using a fan to ameliorate the patient's symptoms was chosen only by the senior physicians (17.1\% vs. 0\%, \( p=0.036 \)). Opening a window was selected by 29.3\% of the senior physicians and 17.4\% of the physicians in training \( (p=0.299) \).

Pharmacological treatment options: Supplemental oxygen was the most important therapeutic approach chosen, with 92.7\% of senior physicians and 95.7\% of physicians in training ranking this as first-line therapy with no significant difference between the groups \( (p=1) \). The second most frequent drug chosen was the application of a ß-2 agonist chosen by 28\% of the senior physicians and 21.7\% of the physicians
in training (p=0.606). Corticosteroids would be used by 25.6% of the senior physicians and by 43.5% of the physicians in training (p=0.122). Regarding opioids, intravenous application was chosen by 43.9% of the senior physicians and 21.7% of the physicians in training (p=0.089), whereas subcutaneous application was chosen by 48.8% of the senior physicians and 78.3% of the physicians in training (p=0.017). Oral application was an option for 9.8% of the senior physicians and 8.7% of the physicians in training (p=1). Intravenous application of benzodiazepines was chosen by 24.4% of the senior physicians and 13% of the physicians in training (p=0.392). Oral application of benzodiazepines was chosen by 7.3% of the senior physicians and 7.6% of the physicians in training (p=1). The subcutaneous route was chosen by 2.4% of the senior physicians and none of the physicians in training (p=1). Anticholinergic drugs were considered by 12.2% of the senior physicians and 4.3% of the physicians in training (p=0.449). Blood transfusions, promethazine, nitroglycerine, heparin, diuretics, antibiotics, chlorpromazine, and methylxanthines were considered by far less than 10% of both groups (Table 2).
Table 2
Frequency of chosen therapeutic options – Therapeutic option vs. level of training (senior physicians vs. physicians in training)

| Therapeutic option         | Senior physicians (n=82) | Physicians in training (n=23) n (%) | p-value* |
|----------------------------|--------------------------|------------------------------------|----------|
|                            | No (n)                   | Yes (n)                            |          |
| Antibiotics                | 81 (98.8)                | 1 (1.2)                            |          |
| Anticholinergic drugs      | 72 (87.8)                | 10 (12.2)                          | 0.449    |
| Benzodiazepines i.v.       | 62 (75.6)                | 20 (24.4)                          | 0.392    |
| Benzodiazepines p.o.       | 76 (92.7)                | 6 (7.3)                            |          |
| Benzodiazepines s.c.       | 80 (97.6)                | 2 (2.4)                            |          |
| Chlorpromazine             | 82 (100)                 | 0                                  | n.a.     |
| Corticosteroids            | 61 (74.4)                | 21 (25.6)                          | 0.122    |
| Diuretics                  | 78 (95.1)                | 4 (4.9)                            |          |
| Fan                        | 68 (82.9)                | 14 (17.1)                          | 0.036    |
| Heparin                    | 80 (97.6)                | 2 (2.4)                            | 0.528    |
| Improvement of position    | 28 (34.1)                | 54 (65.9)                          | 0.004    |
| Methylxanthines            | 81 (98.8)                | 1 (1.2)                            | 0.392    |
| Nitroglycerine             | 80 (97.6)                | 2 (2.4)                            | 0.208    |
| Open window                | 58 (70.7)                | 24 (29.3)                          | 0.299    |
| Opioids i.v.               | 46 (56.1)                | 36 (43.9)                          | 0.089    |
| Opioids p.o.               | 74 (90.2)                | 8 (9.8)                             |          |
| Opioids s.c.               | 42 (51.2)                | 40 (48.8)                          | 0.017    |
| Oxygen                     | 6 (7.3)                  | 76 (92.7)                          |          |
| Promethazine               | 82 (100)                 | 0                                  | n.a.     |

*Fisher’s exact test was applied.

i.v.: intravenously; n.a.: not applicable; p.o.: orally; s.c.: subcutaneously.

Adapted from Chan K.-S., Sham, M., Tse, D et al. (2005). Palliative medicine in malignant respiratory disease. The Oxford textbook of palliative care (pp. 587–618). Editors: N. Cherny, M. Fallon, S. Kaasa, R.K. Portenoy, DC Currow. Oxford University Press.
| Therapeutic option | Senior physicians (n=82) | Physicians in training (n= 23) | p-value* |
|-------------------|--------------------------|-----------------------------|----------|
|                   | n (%)                    | n (%)                       |          |
| Psychological support | 22 (26.8)                | 6 (26.1)                    | 1        |
| ß-2-agonists       | 59 (72.0)                | 23 (28.0)                   | 0.606    |
| Transfusions       | 82 (100)                 | 0                            | 0.219    |

*Fisher’s exact test was applied.

i.v.: intravenously; n.a.: not applicable; p.o.: orally; s.c.: subcutaneously.

Adapted from Chan K.-S., Sham, M., Tse, D et al. (2005). Palliative medicine in malignant respiratory disease. The Oxford textbook of palliative care (pp. 587–618). Editors: N. Chemy, M. Fallon, S. Kaasa, R.K. Portenoy, DC Currow. Oxford University Press.

**Discussion**

The major goal of this study was to evaluate physicians’ attitudes toward diagnostic approaches and the treatment of severe acute dyspnea in a patient with advanced cancer. The main findings showed that evidence-based first-line therapy with opioids was not the first choice of experienced senior physicians or physicians in training. Both groups of MDs ranked oxygen therapy and betamimetics as first-line treatment options. Furthermore, comparing the choices of different diagnostic options between the groups revealed a significant difference for the use of blood gas analysis (p=0.01), measuring oxygen saturation (p=0.048), and a trend toward a difference for auscultation.

In severely ill patients, appropriate symptom alleviation is the cornerstone of good medical care, and diagnostic procedures should always be accompanied by a consideration of their clinical consequences. Auscultation was chosen by almost all the senior physicians, whereas only about 80% of the physicians in training considered this to be an important diagnostic tool (p=0.076). Percussion was chosen rarely by both groups (37.8% of senior doctors vs. 25.0% of physicians in training, p=not significant). Other first-line investigations did not show any significant differences between the two groups. The measurement of oxygen saturation is often used in the assessment of dyspnea, but it is of limited value [5]. However, 82.9% of the senior physicians, but only 62.5% of the physicians in training, would choose this option (p=0.01). Second-line and third-line investigations, were only rarely chosen by both groups.

Our study also showed differences in the ranking and use of therapeutic options. Whereas the treatment of pain with opioids has become routine not only for doctors familiar with the concepts of palliative care, dyspnea in patients with advanced cancer or other palliative care situations remains difficult. Respiratory depression is a major concern, leading to the restrained application of opioids in this situation [27]. Borasio et al. evaluated attitudes toward patient care at the end of life by surveying 411 medical directors of neurological departments in Germany. The results revealed that 32% thought that it was illegal to
administer analgesics in doses that risk respiratory depression, and 45% believed that treating terminal dyspnea with morphine was the same as euthanasia [28]. A French study asked 791 general practitioners and oncologists whether they would prescribe morphine as a first-line therapy to patients with terminal lung cancer suffering from dyspnea associated with cough and great anxiety. Half of the oncologists and 40% of the general practitioners stated that they would prescribe morphine in the presented case. The prescriptive attitude correlated with the physician’s age, professional background, communication skills, and attitudes toward terminally ill patients [29]. In our evaluation, 9.5% of all the MDs would apply opioids orally, 55.2% subcutaneously, and 39% intravenously in the presented case of a patient with advanced lung cancer and refractory dyspnea.

In summary, the management of dyspnea in terminally ill patients might often be inadequate [28, 29]. There is no higher risk of respiratory depression or increase of pCO₂, even in opioid-naïve patients [30, 31]. In addition to non-pharmacological therapies, the only validated treatment for ameliorating patients’ dyspnea is opioids administered either orally or parenterally [7, 32]. Thus far, no data support the assumption that the use of opioids for dyspnea management is associated with a reduction in the patient’s life expectancy. On the contrary, patients who receive appropriate symptom management might have prolonged survival due to a reduction in physical and psychological stress and exhaustion [11]. In cancer patients, the adverse effects of opioids, such as sleepiness, hypercapnia, or nausea, are infrequent, and the occurrence of transient sedation may also be related to sleep deprivation due to uncontrolled dyspnea [24]. Conversely, despite the use of opioids to control dyspnea, there have been no controlled trials to compare the efficacy of various agents, routes of administration, the starting dose, and the optimal dosage. A few controlled trials with low sample sizes studied the use of morphine in cancer patients, administered orally, subcutaneously, intravenously, intramuscularly, or nebulized [33–37]. Thus, it remains unclear which opioid is most effective and whether there are differences between the agents. Furthermore, data about the optimal starting dose and the best mode of application need to be evaluated in larger randomized trials [5]. Interestingly, in our study, the physicians in training would apply opioids subcutaneously significantly more often than the senior physicians (p=0.017).

Next to opioids, our study also explored the use of additional pharmacologic treatment options. Although no data support the use of bronchodilators (e.g., β-2 agonists) as a first-line treatment, 28 of the physicians in training chose this option, maybe by assuming a bronchospastic component as an explanation of the patient’s dyspnea. Another explanation could be that physicians in training are less reluctant to use a bronchodilator than an opioid. Regarding benzodiazepines, 32.5% of all the participating MDs would apply these drugs in the given scenario. So far, there is no evidence of a beneficial effect of benzodiazepines in controlling dyspnea, although recent research has concluded that midazolam as an upfront therapy might be beneficial for patients [9, 38–40]. However, a Cochrane review recommended the use of benzodiazepines only if first-line treatment has failed [38].

Oxygen as the initial therapeutic approach was ranked first in both groups and was among the treatment options chosen by 93.3% of all the MDs. In advanced cancer patients, two randomized studies compared the effects of supplemental oxygen and ambient air on dyspnea. Oxygen significantly increased oxygen
saturation compared to ambient air in hypoxemic cancer patients at rest [24]. However, Booth et al. reported that ambient air was just as effective as oxygen in relieving dyspnea [41]. Until now, there have been no consensus guidelines on the use of supplemental oxygen for dyspneic cancer patients, but it appears reasonable to apply this option in dyspneic cancer patients with hypoxemia.

Finally, a previous study evaluated the attitudes of fourth-year medical students toward diagnostic and therapeutic approaches in a similar situation. Among the 423 participants, 92% considered oxygen the most important treatment option. However, 32.6% would also suggest the use of opioids as an option, which is comparable to our study results [42].

**Conclusion**

Recent guidelines recommend the use of opioids as a first-line pharmacological treatment for cancer patients with severe dyspnea [8, 9]. Our study revealed that opioids to alleviate dyspnea in this scenario were only an option for less than half of the participating physicians.

Most physicians know that opioids may depress respiration, particularly in opioid-naive patients. The exact mechanism of this respiratory depressant effect remains unclear and might be due to a reduction in the sensitivity and responsiveness of the medullary respiratory centers to hypoxia and hypercapnia [43]. Opioids reduce minute ventilation by slowing the respiratory rate and decreasing the tidal volume [44]. Not only physicians in training but also senior physicians should be taught that there is no evidence for respiratory depression when carefully using opioids to manage dyspnea-related symptoms. Chronic ventilatory failure appears to be neither common nor clinically significant in advanced cancer patients [45].

Our study results confirm the need for proper education of physicians in the diagnosis and management of dyspnea in cancer patients. The management of dyspnea might sound complex, but implementing a comprehensive assessment, discussing goals of care, and applying appropriate pharmacologic and non-pharmacologic interventions may positively impact the quality of life for patients with dyspnea in a palliative care setting.

**Abbreviations**

MDs = medical doctors

UICC = Union for International Cancer Control

**Declarations**

**Acknowledgments**

We are sincerely grateful to the physicians who volunteered to participate in this study.
Funding

We acknowledge support from the Open Access Publishing Fund of Karl Landsteiner University of Health Sciences, Krems, Austria.

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest and no competing interests.

Availability of data and material

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Code availability

Data analysis was performed using the statistical program Microsoft Office Excel (version 15.27) and IBM SPSS Statistics (version 27, Armonk, NY, USA).

Authors’ contribution

MH, EKM, MP, and GK provided the overall conception and design of the study. MH, GR, MS, SD, and GK provided the participants. KH and MW assisted with administrative support. MH, MW, SD, and GK collected and assembled the data. KH, MH, MW, and GK performed all data analysis. KH, and GK wrote the article. All authors read and approved the final article.

Ethics approval

For the present study, as no patient data were involved, assessment by and permission from an ethics committee was not required, as confirmed by the local ethics committee of Karl Landsteiner University of Health Sciences.

Consent to participate

Not applicable

Consent for publication

Not applicable

References

1. Bruera E, Schmitz B, Pither J, Neumann CM, Hanson J (2000) The frequency and correlates of dyspnea in patients with advanced cancer J Pain Symptom Manage 19: 357-362
2. Dudgeon DJ, Lertzman M, Askew GR (2001) Physiological changes and clinical correlations of dyspnea in cancer outpatients J Pain Symptom Manage 21: 373-379

3. Higginson I, McCarthy M (1989) Measuring symptoms in terminal cancer: are pain and dyspnoea controlled? J R Soc Med 82: 264-267

4. Mercadante S, Casuccio A, Fulfaró F (2000) The course of symptom frequency and intensity in advanced cancer patients followed at home J Pain Symptom Manage 20: 104-112

5. Simon ST, Bausewein C (2009) Management of refractory breathlessness in patients with advanced cancer 159: 591-598

6. Viola R, Kiteley C, Lloyd NS, Mackay JA, Wilson J, Wong RKS, Supportive Care Guidelines Group of the Cancer Care Ontario Program in Evidence-Based C (2008) The management of dyspnea in cancer patients: a systematic review Support Care Cancer 16: 329-337

7. Jennings AL, Davies AN, Higgins JPT, Gibbs JSR, Broadley KE (2002) A systematic review of the use of opioids in the management of dyspnea Thorax 57: 939-944

8. Hui D, Bohlke K, Bao T, Campbell TC, Coyne PJ, Currow DC, Gupta A, Leiser AL, Mori M, Nava S, Reinke LF, Roeland EJ, Seigel C, Walsh D, Campbell ML (2021) Management of Dyspnea in Advanced Cancer: ASCO Guideline J Clin Oncol 39: 1389-1411

9. Hui D, Maddocks M, Johnson MJ, Ekstrom M, Simon ST, Ogliari AC, Booth S, Ripamonti C, clinicalguidelines@esmo.org EGCEa (2020) Management of breathlessness in patients with cancer: ESMO Clinical Practice Guidelines(dagger) ESMO Open 5: e001038

10. Chan K, Sham M, Tse D, Thorsen AB (2004) Palliative medicine in malignant respiratory diseases. In: Editor (ed)^(eds) Book Palliative medicine in malignant respiratory diseases. Oxford textbook of palliative medicine, 3rd ed. New York: Oxford University ..., City.

11. Arrieta O, Nunez-Valencia C, Reynoso-Erazo L, Alvarado S, Flores-Estrada D, Angulo LP, Onate-Ocana LF (2012) Health-related quality of life in patients with lung cancer: validation of the Mexican-Spanish version and association with prognosis of the EORTC QLQ-LC13 questionnaire 77: 205-211

12. Corner J, Plant H, A'Hern R, Bailey C (1996) Non-pharmacological intervention for breathlessness in lung cancer Palliat Med 10: 299-305

13. Bausewein C, Booth S, Gysels M, Higginson I (2008) Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases Cochrane Database Syst Rev: CD005623

14. Kemp C (1997) Palliative care for respiratory problems in terminal illness Am J Hosp Palliat Care 14: 26-30

15. Pan CX, Morrison RS, Ness J, Fugh-Berman A, Leipzig RM (2000) Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life. A systematic review J Pain Symptom Manage 20: 374-387

16. Thomas JR, von Gunten CF (2002) Clinical management of dyspnoea Lancet Oncol 3: 223-228
17. Bruera E, MacEachern T, Ripamonti C, Hanson J (1993) Subcutaneous morphine for dyspnea in cancer patients Ann Intern Med 119: 906-907
18. Davis CL (1997) ABC of palliative care. Breathlessness, cough, and other respiratory problems 315: 931-934
19. Del Fabbro E, Dalal S, Bruera E (2006) Symptom control in palliative care–Part III: dyspnea and delirium J Palliat Med 9: 422-436
20. Batchelor TT, Taylor LP, Thaler HT, Posner JB, DeAngelis LM (1997) Steroid myopathy in cancer patients Neurology 48: 1234-1238
21. Croxton TL, Weinmann GG, Senior RM, Wise RA, Crapo JD, Buist AS (2003) Clinical research in chronic obstructive pulmonary disease: needs and opportunities Am J Respir Crit Care Med 167: 1142-1149
22. Congleton J, Muers MF (1995) The incidence of airflow obstruction in bronchial carcinoma, its relation to breathlessness, and response to bronchodilator therapy Respir Med 89: 291-296
23. Cachia E, Ahmedzai SH (2008) Breathlessness in cancer patients 44: 1116-1123
24. Bruera E, Schoeller T, MacEachern T (1992) Symptomatic benefit of supplemental oxygen in hypoxemic patients with terminal cancer: the use of the N of 1 randomized controlled trial J Pain Symptom Manage 7: 365-368
25. Cranston JM, Crockett A, Currow D (2008) Oxygen therapy for dyspnoea in adults Cochrane Database Syst Rev: CD004769
26. Uronis HE, Abernethy AP (2008) Oxygen for relief of dyspnea: what is the evidence? Curr Opin Support Palliat Care 2: 89-94
27. Simon ST, Koskeroglu P, Bausewein C (2012) [Pharmacological therapy of refractory dyspnoea : a systematic literature review] 26: 515-522
28. Borasio GD, Weltermann B, Voltz R, Reichmann H, Zierz S (2004) [Attitudes towards patient care at the end of life. A survey of directors of neurological departments] Nervenarzt 75: 1187-1193
29. Bendiane MK, Peretti-Watel P, Pegliasco H, Favre R, Galinier A, Lapiana J-M, Obadia Y (2005) Morphine prescription to terminally ill patients with lung cancer and dyspnea: French physicians' attitudes J Opioid Manag 1: 25-30
30. Clemens KE, Quednau I, Klaschik E (2008) Is there a higher risk of respiratory depression in opioid-naive palliative care patients during symptomatic therapy of dyspnea with strong opioids? J Palliat Med 11: 204-216
31. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C (2003) Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea 327: 523-528
32. Ben-Aharon I, Gafter-Gvili A, Paul M, Leibovici L, Stemmer SM (2008) Interventions for alleviating cancer-related dyspnea: a systematic review J Clin Oncol 26: 2396-2404
33. Cohen MH, Anderson AJ, Krasnow SH, Spagnolo SV, Citron ML, Payne M, Fossieck BE, Jr. (1991) Continuous intravenous infusion of morphine for severe dyspnea South Med J 84: 229-234
34. Ventafridda V, Ripamonti C, De Conno F, Tamburini M, Cassileth BR (1990) Symptom prevalence and control during cancer patients' last days of life J Palliat Care 6: 7-11
35. Bruera E, Macmillan K, Pither J, MacDonald RN (1990) Effects of morphine on the dyspnea of terminal cancer patients J Pain Symptom Manage 5: 341-344
36. Boyd KJ, Kelly M (1997) Oral morphine as symptomatic treatment of dyspnoea in patients with advanced cancer Palliat Med 11: 277-281
37. Zeppetella G (1997) Nebulized morphine in the palliation of dyspnoea Palliat Med 11: 267-275
38. Simon ST, Higginson IJ, Booth S, Harding R, Weingartner V, Bausewein C (2016) Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults Cochrane Database Syst Rev 10: CD007354
39. Navigante AH, Cerchietti LCA, Castro MA, Lutteral MA, Cabalar ME (2006) Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer J Pain Symptom Manage 31: 38-47
40. Navigante AH, Castro MA, Cerchietti LC (2010) Morphine versus midazolam as upfront therapy to control dyspnea perception in cancer patients while its underlying cause is sought or treated J Pain Symptom Manage 39: 820-830
41. Booth S, Kelly MJ, Cox NP, Adams L, Guz A (1996) Does oxygen help dyspnea in patients with cancer? Am J Respir Crit Care Med 153: 1515-1518
42. Pohl G, Marosi C, Dieckmann K, Goldner G, Elandt K, Hassler M, Schemper M, Strasser-Weippl K, Nauck F, Gaertner J, Watzke H (2012) Evaluation of diagnostic and treatment approaches towards acute dyspnea in a palliative care setting among medical students at the University of Vienna 162: 18-28
43. Rigg JR (1978) Ventilatory effects and plasma concentration of morphine in man Br J Anaesth 50: 759-765
44. LeGrand SB, Khawam EA, Walsh D, Rivera NI (2003) Opioids, respiratory function, and dyspnea Am J Hosp Palliat Care 20: 57-61
45. Walsh TD (1984) Opiates and respiratory function in advanced cancer Recent Results Cancer Res 89: 115-117

Figures
Figure 1

Investigations in advanced cancer patients with acute dyspnea Adapted from Chan K.-S., Sham, M., Tse, D et al. (2005). Palliative medicine in malignant respiratory disease. The Oxford textbook of palliative care (pp. 587–618). Editors: N. Cherny, M. Fallon, S. Kaasa, R.K. Portenoy, DC Currow. Oxford University Press.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Evaluationdyspneaappendix.docx