Opioids in Cancer - Induced Dyspnea – Friend or Foe?

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Abstract: In patients with advanced cancer, especially during their last weeks of life, the most difficult symptom to relieve is dyspnea. The main question is: are opioids safe in this clinical setting? It is a very important question, especially in the Balkan region, where restrictive legislation for many years has been promoting ophiophobia among many physicians and regulatory barriers regarding access to opioids are still in place. We review the mainstay therapy of dyspnea in cancer patients (opioids, benzodiazepines and non-pharmacological interventions).

Keywords: opioids, dyspnea, cancer, safe.

Many oncologists consider palliative care only as terminal care, which is recommended for patients who are not eligible for palliative chemotherapy (either initially or finally). Symptom management is often considered by them as a secondary chapter of the care plan after all chemotherapy’s raised issues. But for the patients and especially for advanced cancer patients, symptom control is crucial for improving or at least maintaining quality of life. Many people involved in palliative care believe that is more important to add life to years than to add years to life. Nevertheless, we need consistent evidence in this field in order to support our beliefs. In recent years, there has been a growing body of evidence showing that research in palliative care is now a true component of cancer research and palliative care should be offered to every advanced cancer patient in addition to standard oncological therapy. The modern model of palliative cancer care implies a complex approach, including palliative care along anticancer therapy right from the very beginning, switching the focus of care from the curative or life-prolonging approach to the palliative one (Fig. 1). To prove that, we will review below the data from a pivotal randomised trial, published last year in NEJM.

The study was conducted by Jennifer Temel at the Massachusetts General Hospital and randomised 150 patients with newly diagnosed metastatic non-small-cell lung cancer to receive either early palliative care integrated with standard oncologic care, or standard oncologic care alone (1). The primary objective was the change from baseline to 12 weeks in the score on the Trial Outcome Index (TOI), which is the sum of the scores on the quality of life (QoL) lung cancer subscale (LCS) for 7 cardinal symptoms and FACT-L QoL scale. The secondary objectives were the change of mood, the percentage of patients receiving aggressive end-of-life care and overall survival. The primary objective of the study was met, patients assigned to early palliative care having a significant improvement in QoL indicators compared with those assigned to standard care (Fig. 2).

The trial demonstrated also an improvement in depression figures, independent of the use of antidepressive agents, but not in anxiety score (Fig. 3). Also, there were noted effects on end-of-life care, with fewer patients receiving aggressive end-of-life care in the early palliative care group. Aggressive end-of-life care was considered the lack of advance resuscitation directives, no or late referral to hospice care and chemotherapy within 14 days before death. Most interesting, this less aggressive end-of-life care did not
adversely affect survival, but on the contrary, a significant improvement in overall survival was observed (Fig. 4).

An NEJM Speaker’s Editorial considered the Temel study as well designed, well-executed and with clinically relevant end points. Their conclusion was that early palliative medicine referral improved survival by almost 3 months, along with better QoL. The magnitude of the benefit in OS terms is the same as palliative platinum-based chemotherapy in advanced NSCLC. The editors concluded that this study was an example of research that shifts a long-held paradigm that palliative care is the alternative to life prolonging or curative care – what we do when there is nothing more that we can do – rather than as a simultaneously delivered adjunct to disease focused treatment (4).

![Figure 2](image2.png)

**Fig. 2.** Change in Quality of Life from Baseline to 12 weeks in the Temel trial.

![Figure 3](image3.png)

**Fig. 3.** Change in Mood from Baseline to 12 weeks in the Temel trial.

![Figure 4](image4.png)

**Fig. 4.** Overall survival analysis in the Temel study.

After convincing readers that palliative care is meaningful and its benefit should be added to standard oncological care, our focus now turns to an ongoing symptom (dyspnea) and the therapeutic approaches used for controlling this symptom are reviewed. Dyspnea is a common symptom among cancer patients. Though effort dyspnea is considered to be a normal (physiological) experience, it becomes pathological if it limits normal activities or is associated with incapacitating anxiety (3). Dyspnea is noticed in more than 70% of cancer patients in their last weeks of life, being severe in almost 25% of those in their last week (4).

The most challenging cases for symptom control are probably advanced cancer patients with severe dyspnea NOT due to massive pleural effusion. Killing the symptom
without killing the patient may be a great challenge for many physicians, who are reluctant to use some drugs such as opioids and benzodiazepines, especially for safety concerns (fear of respiratory depression). The use of opioids in the therapy of dyspnea might sound close to “malpraxis” for many oncologists, especially from Eastern European countries, because of a long lasting restrictive legislation promoting opio-phobia. The lack of proper palliative care training during medical studies and oncology fellowship induce also some degree of opio-phobia. Additionally, there are some regulation barriers for access to opioids, especially in some Eastern European countries.

The biological rationale for using opioids in the therapy of dyspnea is the direct effect of opioids on opioid receptors in the central nervous system, which alter the recognition of breathlessness and the fact that opioids also diminish ventilatory responses, particularly to hypercapnia and less to hypoxia.

There are some pivotal trials of using opioids for dyspnea – the first one published in 1993 by E. Bruera from the MD Anderson Cancer Center, who first introduced subcutaneous morphine in the treatment of dyspnea in cancer patients (5). There are another two important randomised clinical trials, published in 1999 by Mazzocato (6) and Allard (7), which studied the effect of morphine or supplementary doses of opioids for dyspnea, respectively.

A systematic review on this topic (interventions for alleviating cancer-related dyspnea) was published by Ben Aharon in 2008 in the Journal of Clinical Oncology (8). After an extensive research, she found 8 randomised controlled trials (RCTs) with opioid therapy for dyspnea in cancer patients. There were 4 types of RCT design: systemic opioids vs placebo, nebulized opioids vs placebo, nebulized vs systemic opioids and opioid dose escalation. The overall HR of opioid treatment in dyspnea was 1.31, which means that dyspnea scores were improved with 31% compared with placebo. Adverse events were reported in three of the eight selected trials included in the systematic review. There were no significant serious adverse effects noted, such as respiratory depression and sedation. The conclusion of this systematic review was that the administration of subcutaneous morphine resulted in a significant reduction in dyspnea measured by the Visual Analog Scale (VAS), compared with a placebo. And regarding the comparison between nebulized morphine with subcutaneous administration of morphine, there was no difference observed in dyspnea VAS score, although patients preferred the nebulized route (8).

Some might raise the question if there was any detrimental effect on survival by using opioids in treating dyspnea. To answer this question, Sykes performed a systematic review of small studies from palliative-care services in various countries and found no significant difference in survival according to either the absolute morphine dose or a change in morphine dose (9). All studies show that appropriate doses of opioids do not cause respiratory depression. Therefore, caution is advised for patients older than 65 years, during dose titration of the opioid, for patients with abnormal renal function or when concomitant using sedatives. Close monitoring is also very important, especially during titration of opioid dose in opioid-naïve patients. However, the overdosing risk in patients with dyspnea, but without pain, is lower than in patients requiring opioids for pain control, because the dose required for controlling dyspnea is around 50% lower than the dose required for pain control. Common opioid doses used in the therapy of dyspnea are presented in Table I (10).

Another common myth to be challenged is that oxygen supplementation will relieve dyspnea. All current studies and a systematic review on this issue showed that supplemental oxygen was not proved to be superior to room air for alleviating dyspnea, except for patients with hypoxemia. In a palliative care setting, the use of supplemental oxygen is thought to carry adverse effects, including restriction of

<table>
<thead>
<tr>
<th>Opioid-naive pts. &amp; mild dyspnea</th>
<th>Opioid-naive pts. &amp; severe dyspnea</th>
<th>Opioid-tolerant pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine 30 mg orally every 4 h</td>
<td>Morphine sulphate 5 mg orally every 4 h</td>
<td>Increase baseline opioid dose by 25-50%</td>
</tr>
<tr>
<td>For breakthrough symptoms, the same dose every 1-2 h as needed</td>
<td>Oxycodeine 5 mg orally every 4 h</td>
<td>Titrate in increments of 50-100% every 24 h as needed</td>
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<tr>
<td></td>
<td>Hydromorphone 1 mg orally every 4 h</td>
<td>For associated severe COPD, reduce the doses by 50% and titrate with increments of 25%</td>
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<tr>
<td></td>
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activities, possible impairment of the quality of life and psychological dependence, and it is also expensive (8). A recent double-blinded randomized clinical trial, published in 2010, confirms the results of the above cited systematic review. In this trial, 239 patients with refractory dyspnea were randomized between oxygen and room air, both administered via nasal cannula. There was no significant difference between oxygen and room air in relieving dyspnea. The results of this trial confirm that air movement over the face, nose, and nostrils helps to relieve dyspnea. This beneficial effect could be reproduced by using a fan or simply by opening a window (11).

Benzodiazepines are also widely used in the management of dyspnea in cancer patients. Their main effect is mainly by alleviation of anxiety, frequently associated with shortness of breath, which frequently is a factor for worsening dyspnea (12). In a clinical trial on advanced cancer patients with severe dyspnea, reported by Navigante in 2006, addition of midazolam to morphine was significantly more effective than morphine alone, without additional adverse effects. According to a Cochrane review from 2010, benzodiazepines are indicated as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness (13). One widely prescribed regimen for relieving dyspnea, especially in UK, is lorazepam 0.5-1 mg, administered sublingually for a quick onset of action (14).

In conclusion, we might say that palliative care is another weapon in the therapeutic armamentarium used for cancer patients. It can be used in addition with standard oncological treatment (chemotherapy, radiotherapy, surgery, targeted therapy) and will improve the quality of life of advanced cancer patients and perhaps it will improve also their survival. Dyspnea is a common symptom among cancer patients and it is especially important to control it in the last weeks of their life, when is most prevalent and severe. Opioids are the mainstay of treatment of cancer-induced dyspnea not due to massive pleural effusion. Non-pharmacological measures, such as air movement over the face and oxygen for hypoxemic patients, and benzodiazepines are also important in relieving breathlessness.

References

1. Temel JS, Greer JA, et al. Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer, NEJM August 19, 2010; 363;8:733-42

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