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The emerging role of palliative medicine in the treatment of lung cancer patients

ABSTRACT

The symptom burden of patients with lung cancer is extensive and includes loss of appetite, dyspnea, and other symptoms that lead to decreased quality of life. Randomized controlled trial data indicate that early palliative care improves quality of life and depressive symptoms and may extend survival in advanced non–small cell lung cancer compared with standard care. Combining an appetite stimulant (megestrol acetate) with an atypical antipsychotic (olanzapine) leads to greater weight gain and appetite improvement compared with an appetite stimulant alone. Cancer-related dyspnea appears to be a "central" effect that stems from altered afferent inputs in the setting of ventilatory muscle weakness; various treatment options that have shown success in treating cancer-related dyspnea are opioids, tunneled pleural catheters, bilevel positive airway pressure, and nebulized furosemide. Buprenorphine is a unique opioid with activity at mu and nociceptin receptors (also called opioid-receptor-like receptors); it improves pain states dominated by central sensitization.

Several important developments in the palliative care of patients with lung cancer have occurred over the past few years, including publication of a landmark study comparing early with as-needed palliative care, the release of new data on the treatment of cancer-related anorexia, elucidation of new mechanisms and treatment options for dyspnea, and the availability of buprenorphine. This article reviews these emerging concepts.

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LUNG CANCER SYMPTOMS: COMMON AND SEVERE

The symptom burden of lung cancer is usually great. At least 80% of patients experience fatigue, 65% suffer loss of appetite, 77% have cough, 73% report dyspnea (both from local symptoms and weight loss), 57% have chest pain, and 17% have hemoptysis.[1]

When symptoms are present, they are usually severe. Thirty-eight percent of the patients who report fatigue have severe fatigue, 47% have inadequate appetite to the point of requiring intervention, and more than one-half of patients who have chest pain require opioids for relief.[1]

Symptom frequency and severity are worse in individuals who survive 3 months or less.[1] Increasing symptom burden is therefore prognostically important, particularly in patients with advanced stages of lung cancer. As a result, self-assessment of quality of life has a significant ability to predict survival in patients with advanced non–small cell lung cancer (NSCLC).[2]

Patients with lung cancer tend to suffer from groups of symptoms or symptom clusters. Lutz et al[1] found that 79% of patients reported three or more symptoms; these results were similar to the findings of a study by Hollen et al,[3] in which 81% of patients suffered from three or more symptoms, all them severe except for cough.

EARLY PALLIATIVE CARE HAS CLINICAL BENEFITS

A landmark study by Temel et al[4] examined the benefits of early palliative care integrated with standard oncologic care versus standard oncologic care and palliative care only "as needed" on patient-reported outcomes, the use of health services, and the quality of end-of-life care among patients with metastatic NSCLC. The study was a prospective, nonblinded, randomized, controlled trial of outpatients conducted at a single center. The intervention was based on guidelines from the National Consensus Project for Quality Palliative Care, with specific attention to symptom management, goals of care, decision-mak-

TABLE 1
Bivariate analyses of quality-of-life outcomes at 12 weeks

Variable	Standard care (N = 47)	Early palliative care (N = 60)	Difference between standard and early care (95% CI)	*P* value	Effect size
FACT-L score	91.5 ± 15.8	98.0 ± 15.1	6.5 (0.5–12.4)	.03	0.42
LCS score	19.3 ± 4.2	21.0 ± 3.9	1.7 (0.1–3.2)	.04	0.41
TOI score	53.0 ± 11.5	59.0 ± 11.6	6.0 (1.5–10.4)	.009	0.52

CI = confidence interval; FACT-L = Functional Assessment of Cancer Therapy-Lung; LCS = lung cancer subscale; TOI = Trial Outcome Index

ing regarding treatment, and coordination of care. Patients assigned to the intervention met monthly with both a palliative care service and an oncologist, and 90% of the patients randomized to intervention complied with at least 50% of the visits.

Measures of health-related quality of life and mood were obtained using the Functional Assessment of Cancer Therapy-Lung (FACT-L), the Hospital Anxiety and Depression Scale, and the 9-item depression scale of the Patient Health Questionnaire.

Measures of health care service utilization included use of antitumor therapy within 14 days of death, late or no referral to hospice, hospital admissions, and emergency room visits. Patients were considered to have received aggressive care if they met any one of the following three criteria: chemotherapy within 14 days of death, no hospice care, or admission to hospice within 3 days of death.

Quality of life scores improved significantly in patients assigned to intervention compared with standard care **(Table 1)**. The mean improvement in the Trial Outcome Index, which is the sum of the scores on the lung cancer and physical and functional well-being subscales of the FACT-L scale, was 6 points higher in the early palliative care group compared with the standard care group at 12 weeks. The benefits were not only statistically but also clinically significant.

Compared with standard care, early palliative care was associated with an increase in the number of advance directives, earlier hospice referral (11 days vs 4 days), fewer hospitalizations and emergency room visits, and fewer instances of inappropriate oncologic care (defined as chemotherapy within 14 days of death). The percentage of patients with depressed mood was also lower among those assigned to early palliative care versus standard care (16% vs 38%).

A 2.7-month difference in median survival (P = .02) in favor of the group assigned to early palliative care was also observed, although survival was not a primary end point of the trial. This outcome needs to be validated in future studies.

CANCER-RELATED ANOREXIA AND CACHEXIA: TREATMENT IMPROVES APPETITE

The main hallmark of cancer-related anorexia and cachexia is weight loss; this symptom cluster is most often associated with hypophagia. The coexistence of anorexia and appetite-related anhedonia is common in lung cancer patients, such that 25% of lung cancer patients with anorexia report no distress with not eating, nor do they derive pleasure from eating. Others report that early satiety and changes in taste dramatically affect appetite. To some, anorexia is a distressful reminder of progression of their cancer.

Megestrol acetate and medroxyprogesterone acetate at least partially improve appetite in a subset of anorectic cancer patients. The use of medroxyprogesterone acetate has resulted in weight gain but not muscle mass in some patients with cancer-related anorexia, but has had less effect on fatigue and quality of life in these patients.

Olanzapine is an atypical antipsychotic with an affinity for multiple neurotransmitter receptors. Several of these, such as the serotonin receptors 5-HT_2 and 5-HT_3, histamine receptors, and dopamine receptors, are implicated in anorexia, nausea, and vomiting. Case reports suggest that olanzapine has antiemetic activity in patients with advanced cancer and usefulness as prophylaxis against chemotherapy-related nausea and vomiting.[5] Reduced risk of extrapyramidal symptoms compared with standard antiemetics enhances the value of olanzapine for prevention of cancer-related anorexia.

Navari et al[6] conducted a randomized trial to determine the effectiveness of megestrol acetate and olanzapine for the treatment of cancer-related anorexia. Eighty patients were randomized to receive oral megestrol acetate 800 mg/d, or oral megestrol acetate 800 mg/d plus olanzapine 5 mg once nightly, for 8 weeks. Patients were removed from the study if they did not take the study medication for a 48-hour period or if intolerable toxicity developed that was attributable to the study agents.

The MD Anderson Symptom Inventory (MDASI) was completed weekly to assess key symptom outcome variables. A change of 3 cm on the visual analog scale over two separate time periods for a symptom was considered sufficient to define a change in the symptom.

Quality of life was measured using a valid 28-item self-reported instrument (Functional Assessment of Cancer Therapy-General). Patients were examined by their physicians every 2 weeks.

In the group assigned to megestrol acetate, 15 patients had a weight gain of at least 5%—a change that was considered significant. Appetite improved in two patients, nausea decreased in three patients, and quality of life improved in five patients at both 4 weeks and 8 weeks. The improvements in appetite, nausea, and quality of life for the whole group on megestrol acetate alone were not significant, and there was no improvement in mean symptom scores measured by the MDASI.

There were incremental improvements of all measures in patients randomized to megestrol acetate plus olanzapine. Among patients receiving the combination, 33 had a weight gain of at least 5%; 25 reported an improvement in appetite, 21 experienced a reduction in nausea, and 23 had an improvement in quality of life at both 4 weeks and 8 weeks. All outcome variables were improved on the MDASI

CANCER AND DYSPNEA: NUMEROUS INTERVENTIONS HAVE BEEN ASSESSED

Reduced inspiratory capacity caused by weakened inspiratory muscles results in an increased Borg rating of perceived exertion (RPE) relative to oxygen levels. Both central nervous system activation of muscle and loss of muscle tissue contribute to dyspnea and fatigue in lung cancer patients.[7] Cancer fatigue, also measured by the Borg RPE scale, appears to be a "central" mechanism that stems from a mismatch between efferent output for afferent inputs in the setting of ventilatory muscle weakness, thereby increasing the perception of dyspnea. Several interventions have been used to relieve dyspnea, ranging from oxygen therapy to treatment with opioids.

Oxygen saturation

The association between hypoxemia and dyspnea is poor.[8] In a randomized prospective trial, Abernethy et al[9] found no benefit to oxygen therapy compared with medical air without added supplemental oxygen in individuals who had normal oxygen saturation but symptomatic dyspnea.

Bilevel positive airway pressure

Bilevel positive airway pressure has been shown to reduce the need for invasive ventilation; improve oxygen saturation; and reduce dynamic hyperinflation, thus relieving dyspnea.[10] It has been effective in dyspneic patients with motor neuron disease, cancer, heart failure, status asthmaticus, stroke, drug overdose, and interstitial lung disease.

Indwelling pleural catheters

Tunneled pleural catheters reduce the severity of dyspnea in 95% of patients.[11] These catheters are inserted on an outpatient basis, allowing for outpatient drainage. Autopleurodesis occurs in about 45% of patients, in which case the catheter can be removed. Adverse reactions are few (incidence < 10%), but consist of empyema, pneumothorax, cellulitis, or catheter obstruction. The disadvantage is the expense of catheter maintenance.

Nebulized furosemide

Case reports suggest that inhalation of nebulized furosemide, 20 mg four times daily, dramatically improves dyspnea in patients with advanced cancer and severe shortness of breath that is unresponsive to opioids.[12] Nebulized furosemide appears to have a direct effect on either pulmonary stretch receptors or irritant receptors in the airways; it also has a diuretic effect. Response occurs quickly with an onset of effect in 20 to 30 minutes.

B-type natriuretic peptide

The level of N-terminal precursor of B-type natriuretic peptide (NT-pro-BNP) can predict response to sunitinib in renal cancer,[13] and the BNP level predicts 30-day mortality in pulmonary embolism.[14] Measurement of BNP to detect dyspnea in patients with lung cancer is not useful, however, because the BNP level increases with cardiac and pericardial metastases. The BNP level is also persistently elevated after chest radiation therapy, and it increases with anthracycline cardiotoxicity. It is not a useful marker for distinguishing pulmonary from nonpulmonary or cardiac from noncardiac causes of dyspnea.

TABLE 2
Comparison of analgesic equivalence by dosage[26,27]

Drug	Dosage		
Buprenorphine SL	0.8 mg/d	1.2 mg/d	1.6 mg/d
Buprenorphine TD	35 µg/h	50 µg/h	70 µg/h
Morphine	60–90 mg/d	90–140 mg/d	140–225 mg/d
Tramadol	300–400 mg/d	450–660 mg/d	600–800 mg/d
Fentanyl	25 µg/h	35.7 µg/h	50 µg/h

SL = sublingual; TD = transdermal

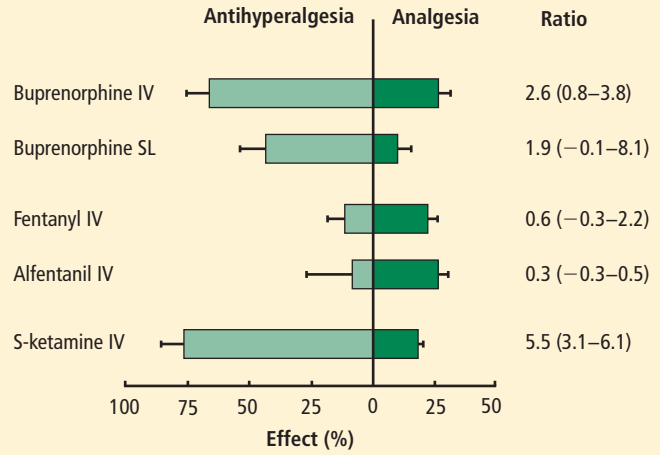

FIGURE. Ratios of antihyperalgesic and analgesic effects for buprenorphine, two pure µ-opioid-receptor agonists (fentanyl and alfentanil), and the *N*-methyl-D-aspartate antagonist ketamine.[25] The ratios were calculated using area-under-the-curve analysis. Buprenorphine and ketamine had higher antihyperalgesia-to-analgesia ratios than the pure µ-opioid-receptor agonists. IV = intravenous; SL = sublingual

Lung ultrasound

Portable diagnostic lung ultrasound can be used to detect pneumonia, pleural effusions, pulmonary emboli, pneumothorax, atelectasis, and lung abscesses as potential causes of dyspnea.[15–18] In addition to the advantage of portability, there is no radiation exposure and the technology permits echocardiography to be conducted.

Opioids

Evidence supports opioids for pharmacologic relief of dyspnea in the palliative care of patients with chronic obstructive pulmonary disease and cancer. Studies have been conducted with morphine sulfate, hydromorphone, dihydrocodeine, intranasal and transmucosal fentanyl, oxycodone, and diamorphine.[19–21]

The response to opioids is unrelated to the severity of dyspnea.[22] Responses and safe administration occur even in patients with reduced oxygen saturation or elevated carbon dioxide partial pressure.[20] Opioids can be used safely in the opioid-naïve population.[20] Recommended dosages in these patients are 2.5 to 5.0 mg of morphine sulfate every 4 hours, 5 mg of oxycodone every 4 hours as needed, and 1 mg of hydromorphone every 4 hours in the opioid-naïve. In opioid-tolerant patients, it is recommended that therapy start with these doses and then be increased in 25% increments every 24 hours, as needed.

BUPRENORPHINE: UNIQUE OPIOID

Buprenorphine is a mu- and nociceptin (ORL-1)-receptor partial agonist with intravenous, subcutaneous, sublingual, transdermal, and intranasal routes of delivery.[23] An agent that acts as an ORL-1 agonist can induce analgesia by blocking nociceptive responses at the level of the spinal cord. It is a kappa antagonist (depending upon the kappa ligand used in the assay), which may contribute to its antihyperalgesia. The parent drug has a high affinity and low intrinsic efficacy for the mu receptor. The main metabolite, norbuprenorphine, is a delta opioid-receptor agonist.

There is a differential dose-response curve for analgesia and respiratory depression with buprenorphine, with less respiratory suppression but no loss of analgesia at high doses. This ceiling effect on respiratory suppression leads to an improved therapeutic index at higher doses; increasing the dosage increases the safety margin.[24] In addition, unlike other potent opioids, buprenorphine does not reduce gonadotropins or sex hormones and is not immunosuppressive. Analgesic potency of sublingual and transdermal buprenorphine is compared with equivalent dosages of morphine, tramadol, and fentanyl in **Table 2**.

Secondary hyperalgesia is an increased sensitivity to painful stimuli around an area of injury and occurs frequently following injury. The increased pain sensation is a result of central sensitization derived from

brainstem neurons that facilitate pain; it is not derived from afferent signals from the primary site. Secondary hyperalgesia is less responsive to opioids than primary hyperalgesia at the site of injury.

Pain is improved with buprenorphine predominantly through modulation of central sensitization and less so at the primary site. Koppert et al[25] demonstrated in human volunteers that buprenorphine reduced the area and duration of secondary hyperalgesia more than pain at the site of injury (half-life of 171 minutes vs 288 minutes, respectively). Buprenorphine had a much greater antihyperalgesic effect than analgesic effect compared with potent opioids such as fentanyl. In contrast, the analgesic effects with fentanyl and alfentanil were much greater than their antihyperalgesic effects **(Figure)**, suggesting the possibility of a combination of opioid therapy for superior pain relief or choices based on pain phenotype (eg, secondary or primary hyperalgesia).

SUMMARY

Early palliative care improves quality of life and decision-making in patients with advanced lung cancer and may improve survival, although survival data need to be confirmed. Olanzapine and megestrol acetate are superior to megestrol acetate alone for the treatment of anorexia. Oxygen is no better than medical air in the management of dyspnea associated with normal oxygen saturation. Buprenorphine is a unique opioid that has value for pharmacologic relief in patients at risk for respiratory depression.

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