November 22, 2019

Stephanie Chang, MD, MPH
Director, EPC Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality
Department of Health and Human Services
Attn: EPC SEADs Coordinator
5600 Fishers Lane
Mail Stop 06E77D
Rockville, MD 20857

RE: Supplemental Evidence and Data Request on Interventions with Dyspnea in Patients with Advanced Cancer

Dear Dr. Chang:

The National Comprehensive Cancer Network® (NCCN®) is pleased to respond to the Agency for Healthcare Research and Quality (AHRQ) Supplemental Evidence and Data Request on Interventions for Dyspnea in Patients with Advanced Cancer. Like AHRQ, NCCN is committed to advancing safe, high quality, equitable, and affordable cancer care through the promotion of evidence-based practice. We will focus our remarks on the evidence available for interventions for dyspnea that is included in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Palliative Care.

NCCN Background

As an alliance of 28 leading academic cancer centers in the United States that treat hundreds of thousands of patients with cancer annually, the NCCN’s mission is to improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives. The NCCN develops and maintains guidelines covering cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals throughout the spectrum of oncologic management, and apply to 97 percent of cancers affecting patients in the United States.

NCCN Guidelines® and Library of Compendia products help ensure access to appropriate care, clinical decision-making, and assessment of quality improvement initiatives. Since 2008, CMS has recognized the NCCN Drugs & Biologics Compendium (NCCN Compendium®) as a mandated reference for establishment of coverage policy and coverage decisions regarding the use of drugs and biologics in cancer care. Commercial payers that represent more than 85 percent of covered lives in the United States also utilize the NCCN Guidelines and Library of Compendia products. The NCCN Guidelines are transparent, continuously updated, available free of charge online for non-commercial use and through a multitude of HIT vendors.
NCCN works with HIT vendors through permissions and licensing arrangements to allow for use of the NCCN Guidelines and the NCCN Compendium® when supporting decision making that impacts patient access to appropriate therapy. NCCN is grateful for the opportunity to respond to this Supplemental Evidence and Data Request and will focus comments on data supporting pharmacological and non-pharmacological interventions.

**Recommended Interventions**

As one of the most common symptoms in patients with advanced lung cancer\(^1\), NCCN appreciates AHRQ’s attention to the evidence available for interventions in the treatment of dyspnea. Evidence for appropriate treatment in advanced stage cancer patients is well established in the NCCN Palliative Care Guidelines Version 2.2019.\(^2\) Appropriate excerpts from the Guidelines are outlined below, including citations for supporting evidence.

Dans et al. (2019) recommend the following:

Potentially reversible underlying causes or comorbid conditions should be treated using chemotherapy or radiation therapy; therapeutic procedures for cardiac, pleural, or abdominal fluid\(^3,4,5\); bronchoscopic therapy; or bronchodilators, diuretics, steroids, antibiotics, transfusions, or anticoagulants for pulmonary emboli. Palliative radiotherapy can be considered for patients with SVC syndrome or those who have respiratory obstruction by tumor mass.\(^6,7\) Both pharmacologic and non-pharmacologic intervention have been investigated in the management of dyspnea...Recommended pharmacologic

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interventions include opioids with or without benzodiazepines. Benzodiazepines can be considered for coexisting anxiety. However, the reported beneficial effect of benzodiazepines on dyspnea in patients with advanced cancer is small, and the addition of benzodiazepines to opioids can increase the risk of respiratory depression.

Of the opioids, morphine has undergone the most extensive investigation for treating dyspnea in patients with cancer; recent studies have also looked at opioids such as fentanyl and oxycodone. Prophylactic fentanyl provided through buccal or subcutaneous routes improved episodic exertional dyspnea in two small randomized, controlled trials in patients with cancer. Nebulized fentanyl has also been studied. A single-institution trial of nebulized fentanyl in patients with cancer with dyspnea showed improved oxygenation and reduced tachypnea, and 79% of patients said it improved their breathing. An attempted randomized, placebo-controlled trial at the same institution was not successful.

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13 Clemens, K. E., 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?. Journal of palliative medicine, 11(2), 204-216.
because the practice had already diffused widely with over 1000 doses being prescribed. Additionally, an observational study of 136 patients with terminal cancer also suggested that continuous infusion of subcutaneous oxycodone may provide relief of dyspnea in addition to pain relief. For patients receiving chronic opioids, the panel recommends consideration of a 25% dose increase to manage dyspnea.

Scopolamine, atropine, hyoscyamine, and glycopyrrolate are options reduce excessive secretions associated with dyspnea. Glycopyrrolate does not effectively cross the blood-brain barrier and is less likely than the other drug options to cause delirium, but this agent can produce anticholinergic side effects. Scopolamine can be administered subcutaneously or transdermally; physicians should be aware that the onset of benefit for transdermal scopolamine patches is about 12 hours, and they thus may not be an appropriate choice for imminently dying patients. A subcutaneous injection of scopolamine can be administered when the patch is applied or if management of secretions is inadequate.

Non-pharmacologic interventions include the use of handheld fans directed at the face, cooler temperatures, supplemental oxygen, and time-limited trials of noninvasive mechanical ventilation if indicated. A randomized controlled trial examined the effects of room air versus palliative oxygen delivered via nasal cannula in patients with refractory dyspnea. Dyspnea scores were no different among patients receiving palliative oxygen versus room air, encouraging the use of less burdensome interventions.

High-flow nasal oxygen and noninvasive mechanical ventilation are not available outside of the hospital setting, but may provide temporary improvements in hypoxemia and dyspnea. In a recent feasibility study of 200 patients with solid tumors randomized to receive either noninvasive positive-pressure ventilation (biphasic positive airway pressure, BiPAP) or conventional oxygen therapy, patients in the ventilation group had greater improvement in dyspnea symptoms and required lower doses of opiates than patients in the oxygen group. A smaller phase II randomized trial comparing high-flow oxygen to BiPAP for persistent dyspnea in patients with advanced cancer revealed no significant differences between the two approaches.

When caring for actively dying patients, providers should discuss the reversibility of respiratory failure and treatment options, and provide anticipatory guidance for patient/family/caregivers(s) about dying of respiratory failure. As life expectancy decreases, the role of mechanical ventilation and noxygens diminishes, and the role of pharmacologic interventions such as opioids, benzodiazepines, glycopyrrolate, and scopolamine increases. If fluid overload is a contributing factor, enteral and parenteral fluids should be

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decreased or discontinued, and low-dose diuretics can be considered. (p. MS-13-MS-14)

NCCN appreciates the opportunity to respond to the AHRQ Supplemental Evidence and Data Request on Interventions for Dyspnea in Patients with Advanced Cancer. We appreciate AHRQ’s commitment to evidence-based care to support cancer patients throughout the care continuum. NCCN encourages AHRQ to consider the NCCN Palliative Care Guidelines as a resource, and we look forward to working together to improve patient access to quality cancer care.

Sincerely,

Robert W. Carlson, MD
Chief Executive Officer
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Palliative care and/or hospice care should not be described as “giving up,” but instead reframed as “fighting” for better quality of life.

In general, patients with weeks to days to live (ie, dying patients) should discontinue all treatments not directly contributing to patient comfort. Intensive palliative care focusing on symptom management should be provided in addition to preparation for the dying process. Refer to hospice when possible.

**Symptom Management**

Special considerations in the implementation of these guidelines based on life expectancy are delineated in the algorithm. The major focus of these special considerations is the withholding and withdrawal of aggressive interventions; prevention and elimination of side effects associated with pharmacologic pain management; the acceptance of loss of function for the sake of relief of symptoms; and the treatment of the unique symptoms of patients in their final hours of life. With regard to symptoms, the management of pain, dyspnea, anorexia/cachexia, nausea and vomiting, constipation, diarrhea, MBO, fatigue, delirium, and psychological distress is fundamental and discussed in detail below. As a general principle, if/when appropriate, providers should try to use palliative interventions that may address multiple symptoms.

**Pain**

See the NCCN Guidelines for Adult Cancer Pain for specific recommendations for pain management and education on opioid safety. Provide education to the family/caregiver on the role of pain medications, customizing the education to the patient’s particular situation. In addition, it is important to note that dying patients in their last weeks of life have several specific requirements. For instance, opioid dose should not be reduced solely for decreased blood pressure, respiration rate, or level of consciousness when opioid is necessary for adequate management of dyspnea and pain. In fact, opioids can be titrated aggressively for moderate/severe acute/chronic pain. In addition, palliative sedation can be considered for refractory pain (see below) following consultation with pain management/palliative care specialists. Short-course palliative RT may be used to address pain associated with bone metastases. Study data suggests that 40% of patients (122/298) who received a single 8 Gy RT dose for painful bone metastases experienced pain reduction and improved quality of life within 10 days.

**Dyspnea**

Dyspnea is one of the most common symptoms in patients with advanced lung cancer. The American Thoracic Society consensus statement defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.” Symptoms should first be comprehensively assessed in all patients. In non-communicative patients with weeks to days to live, symptom intensity should be assessed using physical signs of dyspnea. Education should be provided to the patient/family/caregiver on the patient’s condition and the risk/benefit of treatment options. Potentially reversible underlying causes or comorbid conditions should be treated using chemotherapy or radiation therapy; therapeutic procedures for cardiac, pleural, or abdominal fluid; bronchoscopic therapy; or bronchodilators, diuretics, steroids, antibiotics, transfusions, or anticoagulants for pulmonary emboli. Palliative RT can be considered for patients with SVC syndrome or those who have respiratory obstruction by tumor mass.

Both pharmacologic and non-pharmacologic interventions have been investigated in the management of dyspnea. A review concluded that little definitive data evaluating the effectiveness of dyspnea interventions exist and that randomized controlled trials are needed. Other reviews have determined that there are sufficient data to make treatment recommendations. Recommended pharmacologic interventions...
include opioids with or without benzodiazepines. Benzodiazepines can be considered for coexisting anxiety. However, the reported beneficial effect of benzodiazepines on dyspnea in patients with advanced cancer is small, and the addition of benzodiazepines to opioids can increase the risk of respiratory depression.

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