Building the Palliative Care Evidence Base: Lessons From a Randomized Controlled Trial of Oxygen vs Room Air for Refractory Dyspnea

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Abstract

Palliative care is increasingly seen as a standard component of high-quality comprehensive cancer care. However, several challenges remain to its widespread integration into clinical oncology practice, including workforce problems, reimbursement concerns, and a fledgling evidence base. This article discusses issues surrounding evidence base development in palliative cancer care, using the example of a recently published randomized controlled trial of oxygen versus room air. The Oxygen Trial randomized patients with refractory dyspnea and adequate Pao2 to oxygen or room air, administered via nasal cannula. Both groups experienced improvements in self-rated dyspnea scores, but no statistical differences were seen between intervention arms. These results suggest that supplementary oxygen is often unnecessary in the palliative setting, and that room air is similarly efficacious. This example highlights the importance and need for ongoing development of the evidence base in palliative medicine. The Palliative Care Research Cooperative (PCRC) is a novel National Institute of Nursing Research–funded research infrastructure that seeks to expand the palliative care evidence base. Its first multisite trial was recently completed, assessing the pragmatic question of whether statins can be safely discontinued in end-of-life settings. The PCRC will be a vehicle through which a high-quality evidence base will continue to expand and develop. Such ongoing research efforts are needed to inform and improve palliative care practice. (J Natl Compr Canc Netw 2014;12:989–992)

Palliative care is increasingly seen as a standard component of high-quality, patient-centered comprehensive cancer care. In early 2012, ASCO released its pivotal “provisional clinical opinion” (PCO) statement on this topic, recommending the integration of specialist palliative care services into standard cancer care for those with metastatic or advanced disease, from the time of diagnosis.1 This opinion was rendered in light of newly published practice-changing data from a randomized controlled trial of palliative care in advanced lung cancer that showed improvements in quality of life and survival.2 The PCO reinforced to the oncology community that palliative care is not synonymous with end-of-life care, and that specialist palliative care services constitute a specific high-level skillset that adds something important to the care of patients with advanced cancers or those who have a significant symptom burden.

Although the PCO represents a giant leap forward for patients with cancer and their families, several challenges remain to its implementation. First, being a relatively young medical specialty, palliative medicine faces significant workforce problems. Simply not enough palliative care clinicians are practicing and available to see all the patients who should be seen under the PCO rubric; a recent task force from the American Academy of Hospice and Palliative Medicine (AAHPM) projects a shortage of more than 6000 full-time physicians in the...
field. Second, major reimbursement barriers remain. The lack of an established reimbursement mechanism for outpatient palliative care, for example, can make starting a clinic difficult even when it is clearly needed. Third, being a young field, palliative medicine has a relatively limited evidence base to guide interventions and practice.

This article focuses on the issue of evidence base development in palliative cancer care, using the example of a recently published randomized controlled trial of a commonly used palliative intervention to highlight the importance and need for rigorous clinical trials in this space.

**The Oxygen Trial**

Oxygen is widely used to palliate symptomatic dyspnea in patients with life-limiting illness. However, it is often provided on a “compassionate basis” in palliative settings, because many of these patients are otherwise ineligible for oxygen therapy. Guidelines usually stipulate specific oxygen saturation and/or PaO₂ thresholds for therapeutic oxygen prescribing, which may not be met by patients with refractory dyspnea in the palliative setting. The use of oxygen in patients with advanced illness had not been rigorously tested in a randomized trial setting. It also comes at significant cost. The Oxygen Trial was thus designed to assess the efficacy of oxygen at relieving dyspnea, via a rigorous randomized controlled trial.

**Study Design**

The Oxygen Trial compared oxygen versus room air, both via nasal cannula, for relief of refractory breathlessness in patients with an adequate PaO₂. It occurred across 9 sites in Australia, the United States, and the United Kingdom, in the outpatient setting. Study participants included those with life-limiting illness, refractory dyspnea, and PaO₂ of more than 55 mmHg. Patients were excluded if they met international eligibility guidelines for long-term oxygen therapy, had a history of hypercarbic respiratory failure with oxygen, anemia (hemoglobin <100 g/L), hypercarbia (PaCO₂ >50 mm Hg), or cognitive impairment (Folstein Mini-Mental State Examination score <24/30); were actively smoking; or had a respiratory or cardiac event in the preceding 7 days.

Participants were randomized 1:1 to receive oxygen or room air via a concentrator, through a nasal cannula, at 2 L/min, for 7 days. They were instructed to use the concentrator for at least 15 hours per day. Randomization was stratified by baseline PaO₂, using a block randomization schema, with blocks of 4 patients to ensure even distribution of this key variable among patients in both study arms. The primary outcome measure was dyspnea (“breathlessness,” or “shortness of breath,” depending on the country), measured on a 0 to 10 numerical rating scale, in both the morning and evening. Quality of life was measured using the McGill Quality of Life Questionnaire.

**Results**

A total of 239 patients were randomized; 120 received oxygen and 119 were given room air. Among those assigned to oxygen therapy, 112 (93%) completed all 7 days of assessments, compared with 99 (83%) of those receiving room air. From baseline to day 6, mean morning dyspnea scores changed by −0.9 points (95% CI, −1.3 to −0.5) in participants who were assigned to receive oxygen, and by −0.2 points (−1.2 to 0.2) in those randomized to room air (P=.504). The mean evening dyspnea score changed by −0.3 points (−0.7 to 0.1) in the oxygen group, compared with −0.5 (−0.9 to −0.1) in the room air group (P=.554). Careful review of data trends suggested that all benefit derived in morning or evening dyspnea intensity occurred within the first 3 days. Quality-of-life changes mirrored the trends in dyspnea scores.

No statistically significant differences in side effects were seen between the groups. Extreme drowsiness was reported by 12 (10%) of the patients assigned to receive oxygen compared with 14 (13%) of those randomized to room air. Two (2%) patients in the oxygen group developed significant nasal irritation compared with 7 (6%) in the room air group. One patient in the oxygen group reported very troublesome epistaxis.

Predictors of response were explored; only the intervention and the baseline intensity of dyspnea were predictive. Specifically, being randomized to the oxygen group doubled the chance of dyspnea improvement in the morning (odds ratio [OR], 2.0; 95% CI, 1.1–3.5). Participants with baseline dyspnea scores of 7 or more were more likely to have a response than were participants with baseline dyspnea scores of 0 to 3 (OR, 5.3; 95% CI, 2.2–12.8), or baseline dyspnea scores of 4 to 6 (OR, 3.4; 95% CI, 0.8–3.0).
Interpretation and Implications

The somewhat surprising results of the Oxygen Trial highlight the importance of performing rigorous clinical trials in palliative medicine. For many years clinicians have prescribed oxygen therapy for patients with advanced illness and adequate PaO₂ who are experiencing dyspnea, without evidence demonstrating its benefit. This strategy seems to have added significant cost and inconvenience to patient care, but has provided no appreciable benefit in symptoms.

Many common practices and treatments used in hospice and palliative medicine settings are without rigorous evidence to guide them or support their ongoing use. These therapies may be costly or even harmful, and therefore need to be tested in a rigorous fashion. In this case, if room air via nasal cannula is just as effective and is less expensive to administer, then equivalent quality care can be provided at a lower cost. Other robust evidence suggests that air movement across the nasal passages results in dyspnea relief, even if by placing a fan in front of a patient’s face. This intervention is safe and very cost-effective, and should be one of the initial interventions for dyspnea.

Several practical implications should be considered. In this study, both intervention arms experienced improvement in dyspnea, with people with severe dyspnea deriving the most benefit. Whether this was from the therapeutic effect of air moving near the face or perhaps the placebo effect is unknown. Furthermore, when clinicians were asked why they prescribed palliative oxygen, a common reason was patient or family request. Although providing medical air at 2 L/min via nasal cannula is presumably cheaper and safer than providing concentrated oxygen (especially for the smoking patient), it still may not be the most practical intervention to prescribe; often in palliative settings providers are able to prescribe oxygen therapy or nothing. Hence, the authors suggest that the best first intervention is a handheld or rotating fan, along with opioids (see later discussion). If these are not effective and/or the patient and family request medical gas, then oxygen may still be the most appropriate option. If prescribed, it is important to advise the patient and family to monitor for a change in dyspnea scores in response to the oxygen treatment. Any response should be observed in the first 3 days; after this period, it is safe to discontinue the intervention if no benefit is seen. Patients, families, and home health nurses must be coached about this, however, because the discontinuation of oxygen therapy can be perceived as “withdrawal of life-sustaining treatment”; in this instance it is clearly nothing of the sort, but this is easily misunderstood by laypersons. Some experts may recommend never prescribing oxygen in the setting of an adequate PaO₂, regardless of family requests, in light of clinical trial findings. However, given the trend toward improvements in morning dyspnea and possibly more improvement in patients with severe dyspnea, the authors believe that oxygen remains a reasonable option for a short-term trial in patients in whom dyspnea is particularly refractory and bothersome.

Opioids are an important intervention for refractory dyspnea management in palliative medicine. Compared with room air or the use of a fan, however, opioids have many more potential side effects. Much like for oxygen, the evidence base regarding opioid use for breathlessness was lacking until recently, and was often characterized by significant concern over respiratory depression and carbon dioxide retention. Although the titration of short-acting oral morphine solution has been the traditional method for managing refractory dyspnea in the hospice setting, one study of long-acting morphine showed the safety and efficacy of using this newer and more convenient approach to refractory dyspnea.

Another area of controversy and minimal data is the use of compounded topical preparations for symptom management. This is a relatively common practice in the hospice setting, because many patients are unable to swallow pills near the end of life, and intravenous access is often inappropriately invasive. So-called ABH gel is one such preparation, consisting of Ativan, Benadryl, and haloperidol, aimed at noninvasively relieving nausea and vomiting at the end of life. A recent study demonstrated no appreciable absorption of the Ativan or haloperidol, and only subtherapeutic absorption of Benadryl. Much like the finding that oxygen is no better than room air for relief of refractory dyspnea, these new findings challenge the assumptions about what defines high-quality care in palliative settings. This is not to say that all topical medications are ineffective or inappropriate; to the contrary, robust data suggest that topical nonsteroidal anti-inflammatory drugs can be very effective for improving arthritic pain in nonpalliative settings.
The aforementioned examples make a very good case for rigorous clinical trials in palliative medicine. Challenging the “hospice lore” about how to optimally manage common problems like dyspnea is important in ensuring that increasingly effective, safe, and cost-efficient therapies are provided to patients with serious illness.

Now that “hospice and palliative medicine” is an officially recognized, boarded subspecialty, the development of its evidence base is even more important to its future. Research in end-of-life and advanced illness settings can be challenging, but the aforementioned examples show that it is important and worth pursuing, because it can facilitate change and improve the quality of care provided. The Oxygen Study is an ideal test case to demonstrate the importance of performing rigorous controlled trials of common clinical practices in palliative care. In recognition of this goal, the United States–based Palliative Care Research Cooperative (PCRC) was recently launched, funded by the National Institute of Nursing Research. This first-of-its-kind US palliative care research group just completed its first study, addressing a very practical question regarding discontinuation of statin medications in the setting of serious illness. The PCRC will be a vehicle through which a high-quality evidence base will continue to expand and develop. Ongoing research efforts such as these are needed to inform and improve palliative care practice.

Conclusions

As palliative care is increasingly viewed as a standard component of comprehensive cancer care, a robust, clinically applicable evidence base is necessary to guide care and improve its quality over time. Although research in advanced illness settings can pose unique challenges, these are not insurmountable. Large randomized controlled trials are feasible even in the hospice setting, as demonstrated by the recent completion of the PCRC’s first trial. The Oxygen Study demonstrates the importance of challenging the status quo regarding often-anecdotal evidence in palliative care, and shows how building the evidence base can change and improve practice in a meaningful way for patients and families, even while decreasing the cost of care.

References