Published in final edited form as:

J Natl Compr Canc Netw. 2014 July ; 12(7): 989–992.

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

Thomas W. LeBlanc, M.D., M.A.^{1,2} and Amy P. Abernethy, M.D., Ph.D.^{2,3}

¹Division of Hematologic Malignancies and Cellular Therapy, Department of Medicine, Duke University School of Medicine Durham, NC USA

²Center for Learning Health Care, Duke Clinical Research Institute, Durham, NC USA

³Division of Medical Oncology, Department of Medicine, Duke University School of Medicine, Durham, NC USA

Abstract

Palliative Care is increasingly seen as a standard component of high-quality comprehensive cancer care. However, there remain several challenges to its widespread integration into clinical oncology practice, including workforce problems, reimbursement concerns, and a fledgling evidence base. Here we discuss issues around evidence base development in palliative cancer care, using the example of a recently-published randomized controlled trial of oxygen vs. 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 there were no statistical differences 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 Group (PCRC) is a novel National Institute of Nursing Research-funded research infrastructure that seeks to expand the palliative care evidence base. Its first multi-site trial was recently completed, assessing the pragmatic question of whether statin medications 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.

Keywords

palliative care; dyspnea; oxygen; clinical trials

Introduction

Palliative Care is increasingly seen as a standard component of high-quality, patient-centered comprehensive cancer care. In early 2012 the American Society of Clinical Oncology (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: a randomized controlled trial of palliative care in advanced lung cancer, showing 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.

While the PCO represents a giant leap forward for cancer patients and families, there remain several challenges to its implementation. First, being a relatively young medical specialty, palliative medicine faces significant workforce problems. There are simply not enough palliative care clinicians around 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 over 6,000 full-time physicians in the field.³ Second, there remain major reimbursement barriers. The lack of an established reimbursement mechanism for outpatient palliative care, for example, can make it difficult to start a clinic even when it is clearly needed. Third, being a young field, palliative medicine has a relatively limited evidence base to guide interventions and practice.

Here we will focus 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, as many such patients are otherwise ineligible for oxygen therapy. Guidelines usually stipulate specific O₂ saturation and/or PaO₂ thresholds for therapeutic oxygen prescribing,⁴ 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 vs. room air, both via nasal cannula, for relief of refractory breathlessness in patients with an adequate PaO₂.⁵ It took place across nine sites in Australia, the USA, and the UK, in the outpatient setting. Study participants included those with life-limiting illness, refractory dyspnea, and PaO₂ of over 55mm Hg. 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 ($\text{PaCO}_2 > 50$ mm Hg), cognitive impairment (Folstein mini-mental status examination score <24/30), were actively smoking, or had 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 liters per minute, for 7 days. They were instructed to use the concentrator for at least 15 hours per day. Randomization was stratified by baseline PaO_2 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 upon the country), measured on a 0–10 numerical rating scale, both in the morning and in the evening. Quality of life was measured using the McGill Quality of Life Questionnaire.

Results

There were 239 patients 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 to 99 (83%) of those receiving room air. From baseline to day 6, participants’ mean morning dyspnea scores changed by –0.9 points (95% CI –1.3 to –0.5) in those who were assigned to receive oxygen, and by –0.7 points (–1.2 to –0.2) in patients randomized to the room air arm ($p=0.504$). The mean evening dyspnea score changed by –0.3 points (–0.7 to 0.1) in the oxygen group, compared to –0.5 (–0.9 to –0.1) in the room air group ($p=0.554$). Careful review of data trends suggested that all benefit derived in morning or evening dyspnea intensity was achieved within the first 3 days. Quality of life changes mirrored the trends in dyspnea scores.

There were no statistically significant differences in side-effects between groups. Extreme drowsiness was reported by 12 (10%) of the patients assigned to receive oxygen, compared with 14 (13%) of those randomized to the room air arm. Two (2%) patients in the oxygen group developed significant nasal irritation, compared with seven (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 ≥ 7 were more likely to have a response than were participants with baseline dyspnea scores of 0 to 3 (OR 5.3, 2.2–12.8), or baseline dyspnea scores of 4 to 6 (OR 3.4, 0.8–3.0).

Interpretation and Implications

The somewhat surprising results of the Oxygen Trial highlight the importance of carrying out rigorous clinical trials in palliative medicine. For many years clinicians have prescribed oxygen therapy for dyspneic patients with advanced illness and adequate PaO_2 , without

evidence demonstrating its benefit. It appears that this strategy has added significant cost and inconvenience to patient care, but without appreciable benefit in symptoms.

Many common practices and treatments used in hospice and palliative medicine settings are without rigorous evidence to guide them, or to support their ongoing use. These therapies may be costly or even harmful, so they 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 we can provide equivalent quality care 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.⁶ Such an intervention is safe and very cost effective, and should be one of the initial interventions for dyspnea.

There are several practical implications to consider here. In this study, both intervention arms experienced improvement in dyspnea, and people with severe dyspnea derived the most benefit. This may be due to the therapeutic effect of air moving near the face, or perhaps due to the placebo effect –we cannot know for sure. Furthermore, when clinicians were asked about why they prescribed palliative oxygen, a common reason was patient or family request.⁷ Although the provision of medical air at 2 liters per minute via nasal cannula is presumably cheaper and safer than concentrated oxygen (especially for the smoking patient), it still may not be the most practical intervention to prescribe; often in palliative settings we are able to prescribe oxygen therapy or nothing. Hence, we suggest that the best first intervention is the handheld fan or a rotating fan in the room, along with opioids (see below). 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 time period, it is safe to discontinue the intervention if no benefit is seen. Patients, families, and home health nurses need to be coached about this, however, as the discontinuation of oxygen therapy can be perceived as “withdrawal of life-sustaining treatment” – in this case, 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 towards improvements in morning dyspnea and possibly more improvement in patients with severe dyspnea, we believe that oxygen remains a reasonable option for a short-term trial in cases where dyspnea is particularly refractory and bothersome.

Opioids are an important intervention for refractory dyspnea management in palliative medicine. Compared to room air or the use of a fan, however, opioids have many more potential side effects. Much like oxygen, the evidence base around opioid use for breathlessness was lacking until relatively recently, and was often characterized by significant concern over respiratory depression and CO₂ 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 has demonstrated the safety and efficacy of using this newer and more convenient approach to refractory dyspnea.⁸

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, since many patients are unable to swallow pills near the end of life, and intravenous access is often inappropriately invasive in the last days of life. So-called “ABH gel” is one such preparation, consisting of Ativan®, Benadryl®, and Haloperidol, aimed at non-invasively relieving nausea and vomiting at the end of life. A recent study demonstrated no appreciable absorption of the Ativan® or haloperidol, and only sub-therapeutic absorption of Benadryl®.⁹ Much like the finding that oxygen is no better than room air at relief of refractory dyspnea, these new findings challenge our 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 NSAIDs can be very effective for improving arthritic pain in non-palliative settings.¹⁰

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 we provide increasingly effective, safe, and cost-efficient therapies 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,¹¹ but the aforementioned examples demonstrate that it is important and worth pursuing, as it can facilitate change and improve the quality of care that we provide. The Oxygen Study is an ideal test-case to demonstrate the importance of doing rigorous controlled trials of common clinical practices in palliative care. In recognition of this goal, the US-based Palliative Care Research Cooperative Group (PCRC) was recently launched,^{12,13} funded by the National Institute of Nursing Research. This first-of-its-kind U.S. palliative care research group just completed its first study, addressing a very practical question around the discontinuation of statin medications in the serious illness setting.^{13,14} 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.

Conclusion

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. While 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 of 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

1. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Mar 10; 2012 30(8):880–887. [PubMed: 22312101]
2. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *The New England journal of medicine*. Aug 19; 2010 363(8):733–742. [PubMed: 20818875]
3. Lupu D. American Academy of H, Palliative Medicine Workforce Task F. Estimate of current hospice and palliative medicine physician workforce shortage. *Journal of pain and symptom management*. Dec; 2010 40(6):899–911. [PubMed: 21145468]
4. Celli BR, MacNee W, Force AET. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *The European respiratory journal*. Jun; 2004 23(6):932–946. [PubMed: 15219010]
5. Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet*. Sep 4; 2010 376(9743):784–793. [PubMed: 20816546]
6. Galbraith S, Fagan P, Perkins P, Lynch A, Booth S. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. *Journal of pain and symptom management*. May; 2010 39(5):831–838. [PubMed: 20471544]
7. Breaden K, Phillips J, Agar M, Grbich C, Abernethy AP, Currow DC. The clinical and social dimensions of prescribing palliative home oxygen for refractory dyspnea. *Journal of palliative medicine*. Mar; 2013 16(3):268–273. [PubMed: 23289922]
8. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised, double blind, placebo controlled crossover trial of sustained release morphine for the management of refractory dyspnoea. *Bmj*. Sep 6; 2003 327(7414):523–528. [PubMed: 12958109]
9. Smith TJ, Ritter JK, Poklis JL, et al. ABH gel is not absorbed from the skin of normal volunteers. *Journal of pain and symptom management*. May; 2012 43(5):961–966. [PubMed: 22560361]
10. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *The Cochrane database of systematic reviews*. 2012; 9:CD007400. [PubMed: 22972108]
11. LeBlanc TW, Wheeler JL, Abernethy AP. Research in end-of-life settings: an ethical inquiry. *Journal of pain & palliative care pharmacotherapy*. Sep; 2010 24(3):244–250. [PubMed: 20718645]
12. Abernethy AP, Aziz NM, Basch E, et al. A strategy to advance the evidence base in palliative medicine: formation of a palliative care research cooperative group. *Journal of palliative medicine*. Dec; 2010 13(12):1407–1413. [PubMed: 21105763]
13. Leblanc TW, Kutner JS, Ko D, Wheeler JL, Bull J, Abernethy AP. Developing the evidence base for palliative care: formation of the palliative care research cooperative and its first trial. *Hospital practice*. Aug; 2010 38(5):137–143. [PubMed: 20890063]
14. LeBlanc TW, Kutner JS, Ritchie CS, Abernethy AP. Discontinuation of statins in routine care settings. *Annals of internal medicine*. Jul 2; 2013 159(1):74–75. [PubMed: 23817715]