

Supportive and palliative care for lung cancer patients

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ABSTRACT

Lung cancer patients face poor survival and experience co-occurring chronic physical and psychological symptoms. These symptoms can result in significant burden, impaired physical and social function and poor quality of life. This paper provides a review of evidence based interventions that support best practice supportive and palliative care for patients with lung cancer. Specifically, interventions to manage dyspnoea, one of the most common symptoms experienced by this group, are discussed to illustrate the emerging evidence base in the field. The evidence base for the pharmacological management of dyspnoea report systemic opioids have the best available evidence to support their use. In particular, the evidence strongly supports systemic morphine preferably initiated and continued as a once daily sustained release preparation. Evidence supporting the use of a range of other adjunctive non-pharmacological interventions in managing the symptom is also emerging. Interventions to improve breathing efficiency that have been reported to be effective include pursed lip breathing, diaphragmatic breathing, positioning and pacing techniques. Psychosocial interventions seeking to reduce anxiety and distress can also improve the management of breathlessness although further studies are needed. In addition, evidence reviews have concluded that case management approaches and nurse led follow-up programs are effective in reducing breathlessness and psychological distress, providing a useful model for supporting implementation of evidence based symptom management strategies. Optimal outcomes from supportive and palliative care interventions thus require a multi-level approach, involving interventions at the patient, health professional and health service level.

KEY WORDS

Lung cancer; palliative care; dyspnoea

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Introduction

Lung cancer patients experience multiple symptoms that often co-occur, the most common being dyspnoea, cough, fatigue, pain, anorexia, anxiety and depression. As survival rates for lung cancer are poor (five-year relative survival rates in Australia of 14.1%) (1), these effects often persist over time and intensify as the disease progresses. Studies report that more than 80% of lung cancer patients have multiple symptoms, often experiencing more symptoms and psychological distress than patients with other cancer types (2). It has been estimated that 43% of patients with lung cancer report psychological distress, compared to an

overall prevalence rate of 35% across 14 cancer sites (3). Such symptoms can result in significant burden, impaired physical and social function and poor quality of life. Newly diagnosed lung cancer patients also report feeling shocked and frightened and display a high need for information (4). Given the burdensome nature of this disease, it is not surprising that studies have confirmed that patients with lung cancer report a higher burden of psychological and daily living unmet needs compared with patients who have other types of cancer (5-8). This paper provides a review of evidence based interventions that support best practice supportive and palliative care for patients with lung cancer. Specifically, pharmacological and non-pharmacological interventions to manage dyspnoea, one of the most common symptoms experienced by this group, will be discussed to illustrate the emerging evidence base in the field. The evidence to support interventions that focus specifically on addressing psychological distress and unmet needs is also discussed. In addition, given the complex nature of the health and support needs experienced by patients with lung cancer, we consider recent evidence regarding health service level interventions

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designed to achieve optimal outcomes this population.

Interventions to manage dyspnoea in patients with lung cancer

Pharmacological management of dyspnoea in lung cancer

The evidence base for the pharmacological management of chronic refractory breathlessness is continuing to improve. In this context, chronic is defined as “daily for more than three of the last six months”, and refractory refers to cases where all underlying causes contributing to breathlessness have been assessed as to whether they can be reversed and, if so, whether they should be reversed. Breathlessness in this case is defined as modified Medical Research Council (mMRC) scale 3 or 4--breathless at rest or on minimal exertion such as the basic activities of daily living (dressing, bathing or preparing food). It is likely, however, that people with mMRC scale 2 will also benefit from breathlessness interventions (9,10). The aim of a therapeutic intervention for this population is to reduce symptomatic breathlessness, as breathlessness will rarely be controlled at all times once chronic irreversible underlying causes of the symptom are established. Although this may translate for some people into improved or better maintained levels of function, ultimately the focus is on reducing the subjective experience that we call ‘breathlessness’. It is important, therefore, that both the severity (intensity) of breathlessness and an affective component (the unpleasantness of breathlessness) should be assessed in this context.

Systemic opioids have the best available evidence to support their use in the clinical setting of people with chronic refractory breathlessness. A meta-analysis and an adequately powered, double blind, randomised controlled crossover trial both report the same order of magnitude of benefit (9,11). The major adverse effect in both of these studies was constipation, which should be treated expectantly, with no recorded episodes of respiratory depression. In prospectively done clinical trials, with carefully titrated opioids, patients have not been admitted to hospital with obtundation, respiratory depression nor confusion. Systemic opioids, where morphine has been the most frequently studied medication, are likely to offer the most benefit.

More recent work has followed patients who gained symptomatic benefit from opioids for chronic refractory breathlessness for up to 660 days to explore the long term efficacy of once daily sustained release morphine (12). In this case, between 10-30 mg of oral morphine per 24 hours was used and delivered a sustained benefit for two thirds of patients who were started on the medication. The majority of this sample derived benefit from just 10 mg per 24 hours.

Other opioids are starting to be studied, but the evidence base strongly supports systemic morphine preferably initiated

and continued as a once daily sustained release preparation. In a sub study exploring response to the titration of sustained release morphine for chronic refractory breathlessness, when benefit was derived, there was not only a reduction in breathlessness in the first 24 hours, but continued improvement over the ensuing week (13). This suggests that sustained release morphine should be titrated to effect and, when benefit is gained, further titration delayed for at least one week.

However, the same systematic review did not demonstrate benefit from nebulised opioids, despite the wide-spread presence of opioids receptors in the bronchial tree. This potentially was a type II error and may relate to the way in which opioids were nebulised (14). However, more recent work suggests that opioids delivered at the alveolar level are likely to help reduce chronic refractory breathlessness. A recently reported randomised control trial demonstrated sustained reduction in breathlessness, improved sleep and decreased cough in a relatively small cohort of people who have long term respiratory damage from previous mustard gas exposure (15).

A number of other medications are being studied. A recent systematic review suggested that there may be benefits from nebulised frusemide unrelated to a diuretic effect (16). The first large study of this has recently been reported and suggests that there may be sustained symptomatic benefit by using nebulised frusemide at a dose of 40 mg/4 mls compared to 4 mls of normal saline. This therapy appeared to be well tolerated (17). Of note, the widespread use of benzodiazepines is not supported with current evidence (18). Although one randomised trial suggested symptomatic benefit was generated more quickly with benzodiazepines in the setting of acute breathlessness where a diagnostic workup was required, the trade-off was increased somnolence.

Non-pharmacological management of dyspnoea in lung cancer

In addition to the growing evidence base supporting the role of various pharmacological agents in the management of breathlessness, evidence to support the use of a range of other adjunctive non-pharmacological interventions in managing the symptom is also emerging. Recently a landmark study has reported on the use of non-invasive ventilation in people with chronic refractory breathlessness and advanced disease without overt respiratory failure. Participants were randomised to oxygen or non-invasive ventilation set to support mode. Non-invasive ventilation was well tolerated in people with advanced disease many of whom derived symptomatic benefit at rates greater than those people treated only with oxygen (19). It is a therapy which will require careful ongoing evaluation in order to understand the net effect that such interventions will deliver to patients with chronic refractory breathlessness in the last days or weeks of life.

A number of recent systematic reviews have also reported

benefits from use of behavioural, psychosocial and environmental modification interventions in the management of dyspnoea (20-22). Most studies in this field involve testing of multicomponent interventions, where a range of strategies are combined into a bundled intervention, making it difficult to ascertain specific components that have most benefit. It is also difficult to conclude which groups of patients are most likely to benefit from these complex interventions, as there is significant variation in study samples (21). At least one review has concluded that patients who enroll and complete these types of interventions appear to be in the earlier stages of their disease or have better functional abilities than those who do not complete the study (21). The application of these approaches, and what modifications are required for patients as the disease progresses, has not been well established.

Notwithstanding these limitations, behavioural and psychosocial interventions for patients with lung cancer that have some supporting evidence can be categorised according to two main mechanisms of action (20). These categories include interventions to improve breathing efficiency and interventions targeting the affective component of breathlessness by seeking to reduce anxiety and distress. Interventions to improve breathing efficiency include a range of breathing retraining techniques, with systematic reviews concluding there is good evidence to support the effectiveness of these techniques, including pursed lip breathing, diaphragmatic breathing, 'blow-as-you-go', positioning and pacing techniques (20).

Another review has concluded that evidence supporting the benefits of exercise programs in controlling breathlessness is not conclusive (23). This review of 16 studies on 13 unique patient groups totaling 675 patients with NSCLC concluded that exercise interventions for patients with NSCLC is safe before and after cancer treatment. While not all studies in this review included breathlessness as an outcome, the authors did conclude there were some positive benefits on exercise capacity, symptoms and some domains of health-related quality of life. The majority of the studies reviewed were, however, small case series and focused mostly on patients immediately pre- and post-surgery. The authors concluded, therefore, that further research is required to establish the effect of exercise, especially in the advanced stage of disease, as well as to determine the optimum type and dose of exercise training.

With regard to interventions aiming to reduce distress associated with breathlessness, interventions including relaxation techniques, coping skills training, and general support for patients and their carers have been reported to achieve positive outcomes (20-22). Relaxation techniques in particular are reported to be beneficial, although the acceptability and sustainability of this approach for all patients has not been determined. As with other non-pharmacological interventions, the available Cochrane Reviews recommend further testing to

determine the nature and scope of psychosocial interventions seeking to improve the management of breathlessness (20,22). Application of such techniques also requires careful assessment of a patient's preferences and capacity to implement them.

The use of a hand held fan has been considered in a limited number of studies. This intervention is thought to produce a flow of air which may alter ventilation when directed to the face, although the exact mechanism of this effect is unclear (24). One small randomised controlled trial (RCT) concluded that the effectiveness of the fan could not be proved, although a small group seemed to benefit, not necessarily related to a relief in breathlessness (24). Work is ongoing to evaluate the effectiveness of this approach.

Interventions to manage psychological distress and unmet needs in lung cancer patients

Despite high levels of distress and perceived unmet need experienced by this group, evidence to inform effective psycho-educational and supportive care interventions for lung cancer patients is scarce (25). The probable reason is the considerable challenges faced in conducting trials of complex interventions with this population. Notably, high refusal rates and poor retention have been acknowledged as a significant difficulty in recruiting patients with lung cancer to these trials (26).

Given the high morbidity of people with lung cancer, a focus of work in this area has been on trialing multifaceted intervention targeting the psycho-social well-being of people with lung cancer. In one study, two sessions of nurse-led coaching in progressive muscle relaxation combined with education on self-management of symptoms at the beginning and middle of radiotherapy were compared against usual care in a RCT (n=140). The intervention was demonstrated to be more effective in terms of reducing breathlessness, fatigue and anxiety compared with usual care (27). Another large trial (N=233) of education versus coping skills training for caregivers showed improvements in patient- and caregiver-reported outcomes, including depression and self-efficacy over time for both groups (28). Both interventions were telephone based and the education consisted of basic information on the illness and patient care and coping skills training incorporating relaxation practices, problem-solving and communication. Interpretation of benefits is complicated by the absence of a suitable 'no treatment' control. The most recent trial (n=108) tested whether a tailored, multidisciplinary supportive care program based on systematic needs assessment with two sessions at the commencement and end of treatment was effective in reducing unmet needs and psychological distress and improving quality of life (29). However, due to methodological limitations there were no differences between the two arms.

In summary, available studies of psychosocial and psychoeducational interventions have notable limitations in their

design including selection, attrition and reporting bias, small samples, insufficient intervention dose and/or a lack of a suitable control group. Notwithstanding these limitations, it is highly plausible that psychosocial interventions can reduce distress associated with lung cancer. Such approaches are therefore an important part of a comprehensive management plan for this population, although further research is needed to define the precise nature and scope of these interventions and application in differing patient contexts.

Service delivery models to optimise outcomes for patients with lung cancer

The complex, multidimensional and chronic nature of lung cancer-related symptoms and associated psychological distress requires an approach to care that enables collaboration between a range of health care providers across inpatient and community settings to support consistent implementation of evidence based supportive care interventions. In recent years, a body of evidence has emerged regarding various health service level interventions that have been designed to achieve optimal outcomes for this group. For example, two studies have investigated post-treatment nurse follow-up versus standard physician follow-up. One three-arm study involved a sample size of 166 people with progressive lung cancer who were randomised to receive a specialised oncology home care program delivered by nurses, a standard home care program delivered by a multidisciplinary team or an office care program delivered by physicians (control group) (30). Participants who received one of the two home-based nurse groups had lower symptom distress, but self-perceived health was also poorer in comparison to the physician follow-up (30). Another study compared nurse follow up with physician follow up after the completion of initial treatment. In this study, patients randomised to nurse-led follow up had open access to nurse specialists Monday to Friday and contact through open access clinic, telephone, and message pager service, and telephone assessment or clinic appointment two weeks after baseline, then every four weeks while the patient was stable with no routine investigations. Emphasis was on rapid and comprehensive communication with general practitioners and the primary healthcare team with regular discussion and referral to a medical team on detection of any new symptom or rapid worsening of condition. Patients who received the nurse-led follow up intervention had less severe dyspnea at 3 months and had better scores for emotional functioning and less peripheral neuropathy at 12 months, although no other significant differences in quality of life domains were identified. Patients who received the nurse-led follow up also scored significantly higher compared to conventional follow up patients in satisfaction with the organisation of care, information and education and personal experience of care at 3, 6 and 12 months from baseline.

Importantly, the authors also reported that the pattern of use of services differed between the two groups. Specifically, compared to conventional follow up patients, patients receiving nurse-led follow up had significantly fewer medical consultations with a hospital doctor at three months, had fewer radiographs taken (including chest radiographs) at 3 months and 6 months, and were more likely to have had radiotherapy treatment at 3 months. Additionally, when place of death was known, significantly more patients who received nurse-led follow up than conventional follow up patients died at home rather than in a hospital or hospice. Comparison of the overall costs of care between groups showed no significant differences (31).

Given the poor prognosis associated with lung cancer, and the likely increasing burden of symptoms as the disease progresses, the potential benefits of referral to palliative care services has also been investigated in one recent study. This randomised trial compared the effect of early referral to palliative care for newly diagnosed metastatic non-small cell lung cancer patients alongside standard oncology care with standard oncology care alone. As hypothesised, patients who received early referral to palliative care had better quality of life and less depressive symptoms than those who received standard care alone. Additionally, and perhaps less expectedly, while patients in the early referral group had less aggressive care than those in the standard care alone group, median survival was longer for patients receiving palliative care compared to standard care (11.6 versus 8.9 months) (32). While the study was conducted in one large cancer centre in the US with its unique health system and is yet to be tested in other health care contexts, the findings of the study raise important questions for clinicians and health service managers about the adequacy of existing linkages between specialist oncology and palliative care services.

Implications for practice and research

Patients with lung cancer experience significant symptom burden and will benefit from good supportive and palliative care. Over the past decade, there have been important advances in understanding of pharmacological and non-pharmacological approaches to managing some common symptoms experienced by this group. This is particularly the case for dyspnoea, although some gaps remain in how these interventions are implemented in practice. Other common symptoms are similarly gaining increased attention, although we have focused on dyspnoea in this review to illustrate advances in the field as the evidence base for this symptom has developed more rapidly than for other symptoms. In addition to the clinical approaches reviewed in this paper, research in this field needs to extend to identify service delivery models that enable implementation of best practice supportive and palliative care. For example, evidence reviews highlight that case management approaches and nurse-led follow-up

programs are effective in reducing breathlessness (20,22) and may be useful in reducing symptom and psychological distress (27,30,31). Such models also have the potential to positively influence the way health services are used. Some evidence also exists to support early referral of patients with metastatic lung cancer to palliative care, alongside standard oncology care (32). While such service delivery models have not been tested across differing health care systems, the findings from these studies are noteworthy and their implications for health services are far reaching. To achieve optimal outcomes for patients with lung cancer requiring supportive and palliative interventions, it is important that these health system level reforms be considered.

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