

Effectiveness of palliative care for non-small cell lung cancer (Review)

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Abstract. Lung cancer is the leading cause of cancer mortality worldwide. Despite increases in the survival rate for various types of cancer over the past several decades, lung cancer remains an overwhelmingly lethal disease and the majority of patients succumb to the disease in a short period of time. A number of treatment options are available depending on the stage of lung cancer. The present review focused on palliative care and is associated with stage IIIB and IV of non-small cell lung cancer (NSCLC). Stage IIIB disease is not amenable to curative treatment and for stage IV disease, treatment is palliative in nature, with a focus on increasing survival time, controlling symptoms and improving or maintaining quality of life. Palliative treatment options include chemotherapy, radiotherapy and supportive care. The present review examines the important aspects of palliative therapy with regard to NSCLC.

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1. Introduction

Lung cancers are divided into two main histological subtypes: small cell (SCLCs) and non-small cell lung cancers (NSCLCs).

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These two types represent cancers that grow and respond to treatment in very different ways and are studied and treated as separate diseases. SCLCs account for 15-20% of lung cancers, tend to grow rapidly and are classified as either limited or extensive stage (1,2). NSCLC is a collection of several tumour histologies including adenocarcinoma, squamous-cell and large cell carcinomas (3). NSCLC accounts for 80-85% of all lung cancers and is characterized by retarded growth and spread compared to SCLC (4). NSCLC is staged using the traditional TNM solid tumour staging system, which is based on tumour size, nodal status and presence or absence of metastases (2). TNM staging is used to group NSCLCs more broadly into four stage categories: I, II, III and IV, the first three of which can be subdivided into A and B subtypes. Stage I cancers are confined to the lung and are no larger than 5 cm while stage II cancers may have some limited spread beyond the primary tumour and are no larger than 7 cm (2). Stage IIIA cancers are characterized by greater spread within the lung itself or connected organs (excluding the opposite lung) or lymph nodes on the same side of the chest (2). Stage IIIB cancers are those that have greater spread into connecting organs and/or lymph nodes above the collar bone or on the contralateral side of the body (2). Stage IV consists of disease that has metastasized to the opposite lung, the fluid surrounding the lungs or heart or to other more distant parts of the body, including the brain, liver, and bones (2). Stages III (usually restricted to IIIB) and stage IV are frequently collectively referred to as 'advanced' stage disease. Approximately 34% of patients are diagnosed with stage I or II, 27% are diagnosed with stage III, and 39% are diagnosed with stage IV (5).

2. Palliative care in lung cancer

Palliative care can be broadly defined as care aimed to improve the quality of life (QOL) of individuals suffering from life-threatening illnesses (4). The World Health Organization (WHO) describes palliative care as 'an approach that improves the QOL of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual' (6). Palliative care for NSCLC can be subdivided into two main categories: the first category is supportive (patient-centred) care and the

second category is tumour-directed therapy. Supportive care, which can include antibiotics, corticosteroids, analgesics, antiemetics, transfusions and psychosocial support (7), is targeted directly at improving the wellbeing of the patient. Tumour-directed therapy also aims to improve patient wellbeing but does so indirectly by targeting the cancer itself using strategies that decrease tumour burden, which in turn, improves patient symptoms and wellbeing. Tumour-directed palliative treatment options for NSCLC include palliative chemotherapy and radiotherapy.

For locally advanced unresectable and metastatic NSCLC (stages IIIB and IV, which are unsuitable for curative treatment options), the standard first-line palliative treatment is palliative chemotherapy with supportive care (8,9). Patients not fit enough to undergo chemotherapy are offered supportive care alone. For patients with specific, localized symptoms care may also include a short course of radiotherapy, which has been shown to alleviate symptoms and improve QOL (10).

3. Palliative chemotherapy vs. supportive care alone

Clinical trials have shown a survival advantage of palliative chemotherapy compared to supportive care alone (7). A meta-analysis performed by the Cochrane Collaboration, which included 16 trials and represented over 84% of the patients from all known randomized trials (as of November 2009) reported an absolute median survival improvement of 1.5 months (from 4.5 to 6 months) resulting in an absolute improvement in the one year survival rate of 9% (from 20 to 29%; HR=0.77, 95% CI=0.71-0.83, $p < 0.0001$) for chemotherapy compared to supportive care alone (7). In patients fit enough to undergo modern, standard, platinum-based, two-drug (platinum doublet) combination chemotherapy, the reported median survival times ranged from 7.4 to 11.3 months (11).

4. Comparison of different palliative chemotherapy regimens

A systematic review of first-line systemic chemotherapy for advanced NSCLC included a discussion of 10 previous systematic reviews (12-14) and concluded that platinum-based doublet chemotherapy (PPDC) is the standard of care for first-line chemotherapy, that platinum-based doublets are superior to non-platinum-based chemotherapies (15), platinum agents alone or other agents alone (13), and that none of the standard platinum doublets is clearly superior to any other. Standard palliative, PPDC regimens include cisplatin or carboplatin combined with gemcitabine, vinorelbine, paclitaxel or docetaxel (16).

5. Patient perspective on survival benefit of palliative chemotherapy

While the survival benefit is clear, the magnitude of that benefit is small (17). However, whether such a small gain is important from the patients' perspective remains to be determined. A study of patients previously treated with cisplatin-based chemotherapy for advanced NSCLC reported a median survival threshold for accepting mildly toxic chemotherapy of 4.5 and 9 months for accepting severely toxic chemotherapy (18). When given the choice between supportive care and chemotherapy, only 22% of

those patients selected chemotherapy for its 3-month survival advantage. By contrast, 68% accepted chemotherapy if it substantially reduced the symptoms (18). The limited survival gains achieved and the relative importance patients place on quality over quantity of life underscores the need for data on QOL and symptom implications of palliative chemotherapy (8) and supports the contention that QOL and symptomatic status are important endpoints in their own right when assessing palliative chemotherapy.

6. Impact of palliative chemotherapy on QOL and symptom levels

Traditionally, the primary endpoints in the clinical randomized controlled trial (RCTs) of palliative chemotherapy for advanced NSCLC have been survival and objective tumour response, while QOL and symptom control have been neglected or relegated to secondary objectives (18). Acceptance of QOL measures as important primary endpoints is on the increase and clinical trials of the past decade often report some QOL measurement. In the RCTs that have addressed QOL, a variety of study methods, chemotherapy regimens and measurement instruments have been employed and the ability of chemotherapy to improve QOL is under debate (19). However, the majority of studies using validated QOL tools have reported some QOL (45-49) and symptom benefit (20) in favour of chemotherapy over supportive care alone, or at minimum, no detrimental effect of chemotherapy compared to supportive care (21,22). However, QOL results are usually confined to a few comments regarding whether there was a significant difference between treatment arms or from baseline and a corresponding P-value without any further detail on absolute changes or proportions of patients who obtained improvement or stabilization of their QOL or symptom levels. There is usually no statistically or clinically significant mean change in QOL from baseline (2553-56). It should be noted that given that the natural trajectory of NSCLC for QOL and that symptoms continually decrease, a treatment that merely maintains current QOL and symptom levels and delays progression is considered successful.

7. Conclusion

The abovementioned studies indicate that palliative care has been recommended as the standard of care for patients with advanced NSCLC based on the results of random clinical trials completed over the past several decades. These trials have reported improvement or stabilization in QOL in one half to one third of patients. However, more comprehensive studies are required to investigate the effectiveness of this treatment in the clinic. Additionally, whether the efficacy of palliative care demonstrated in the trials translates into similar levels of effectiveness in routine practice remains to be determined.

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