

Are the data on quality of life and patient reported outcomes from clinical trials of metastatic non-small-cell lung cancer important?

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Core tip: Are the data on quality of life (QOL) and patient reported outcomes (PROs) from clinical trials of metastatic non-small-cell lung cancer important? Yes, they are important if the data of PROs and QOLs questionnaires are collected appropriately with a good patient's compliance.

Abstract

Majority of the patients with advanced non-small-cell lung cancer (NSCLC) experience two or more disease related symptoms, which may have a negative impact on their health-related quality of life (HR QOL). These patients prefer a therapy that would improve disease related symptoms, as opposed or treatment that slightly prolongs their survival without improving symptoms. The improvements of the symptoms augment the significance of improved response rates or progression free survivals. The choice of the questionnaires to evaluate patients-reported outcomes (PROs) and HRQOL benefits and methods of collecting the data and their interpretations are very important and are discussed in this manuscript. PROs and HR QOL outcomes are important in patients with advanced NSCLC only when the data are collected and analyzed correctly. Then they can be viewed as components of the total value of a treatment, providing a comprehensive picture of the benefits and risks of anticancer therapies. Enabling the patients to feel during the last months of their lives more comfortable and not be dependent on their loved ones is a very important task in the treatment of advanced NSCLC.

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INTRODUCTION

Lung cancer is a leading cause of cancer death worldwide for both men and women^[1].

Majority of the patients present at the time of diagnosis with metastatic disease. Of these patients with advanced non-small-cell lung cancer (NSCLC) approximately 90% of patients experience two or more disease related symptoms such as cough, dyspnea, pain and the general symptoms of fatigue and anorexia^[2]. All these symptoms may cause psychological distress and may have a negative impact on a patient's health-related quality of life (HRQOL). High degrees of psychological distress influence the emotional well-being in both patients and their families. It is not surprising that 68% of patients would prefer a therapy that would improve disease-

related symptoms without prolonging life, as opposed to treatment that slightly prolonged survival without improving symptoms^[3].

Treatment can affect a patient's well-being through both symptom control and treatment-related toxicity^[4]. Therefore; treatments which can decrease tumour growth (achieve a tumour response) and at the same time be less toxic, are very important for these patients^[4,5]. It is important for patients to preserve their independence and not be dependent on their loved ones, becoming a burden at the end for their lives^[6-8].

The response to treatment can have an effect on disease-related symptoms and some studies suggest a link between tumour response and symptoms such as cough, dyspnea, chest pain and also systemic symptoms such as fever, anorexia and weight loss^[9-11]. The improvements of these symptoms further augment the significance of improved response rates or progression free survivals (PFS). Median overall survival for most of the patients with metastatic NSCLC is modest, around one year; in epidermal growth factor receptor mutations positive tumors it approaches two years, thus HRQOL and patients-reported outcomes (PROs) carry high importance.

METHODS OF COLLECTING THE DATA

Patient-reported symptoms (outcomes) and HRQOL benefits are usually assessed using the self-administered cancer-specific European Organisation for Research and Treatment of cancer (EORTC) questionnaires QLQ C30^[12] the lung cancer-specific EORTC QLQ-LC 13^[13] and the Euro QOL EQ-5D^[14] questionnaire or FACT-L^[15] (functional assessment of cancer treatment in lung cancer) questionnaire. The QLQ-C30 questionnaire consists of five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain, nausea/vomiting), a global health status/QOL scale and single items, *i.e.*, dyspnea, loss of appetite, constipation, diarrhea, sleep disturbance and financial impact. The QLQ LC 13 questionnaire incorporates one multi-item scale to assess dyspnea and a series of single items assessing cough, pain, sore mouth, dysphagia, peripheral neuropathy, alopecia and use of pain medication. For each scale/item, a linear transformation was applied to standardize the raw score for a range from 0-100, with 100 representing best possible function/QOL for functional scales, and highest burden of symptoms for symptom scales and symptom items.

A 10-point change in an item or domain is perceived to be clinically meaningful^[16]. The percentage of patients who are classified as improved (≥ 10 -point increase for functioning scales and ≥ 10 -point reduction for symptom domains or items from baseline scores) with respect to each of the questionnaires is examined^[16]. In addition, time to deterioration of an item/domain score is defined as the item from randomization to the first appearance of a score that is 10-points or more lower or higher than the baseline score (≥ 10 -point reduction for function-

ing scales and ≥ 10 -point increase for symptom scales or items). The EQ-5D is a disease-generic questionnaire that comprises the EQ-5D and EQ-visual analogue scale (VAS). The EQ-5D measures five dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems and extreme problems). Utility scores range from 0-1 and were calculated from the five EQ-5D items scores using the United Kingdom preference weights^[17]. The EQ-VAS records the patient's self-rated health status on a vertical, graduated (0-100) VAS. Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire (version 4) comprises 36 items across 5 domains/categories, *i.e.*, physical, social, family, emotional and functional well-being. Lung cancer subscale consists of *i.e.*, symptoms, cognitive function and regret of smoking. Scores range from 0 (not at all) to 4 (very much)^[15].

Each protocol specifies schedule for questionnaires to be completed, *i.e.*, at baseline, every 2-4 wk, at the end of treatment visit and during the first follow-up visit. The use of concomitant medications has to be assessed at the baseline and during the trial, especially the analgesic use, anti-anxiety, depression medication, O₂ use, *etc.*

RESULTS AND THEIR INTERPRETATION

In order to obtain reliable results, patients have to answer the questionnaires prior to meeting their physicians and finding out results of their tests (scans). Help with the questionnaires should be available by knowledgeable staff in the clinic/hospital. The questionnaire has to be filled out by the patients themselves, not by other family member. A supervision to ensure objectivity is important.

The attention has to be paid to baseline scores. In randomized trials, are they well balanced? Are they low (= low burden of symptoms) or high (= high burden of symptoms)? If the baseline scores are low, the percentage of patients with improved symptoms on certain anti-cancer treatment might be difficult to find. On the other hand, time to symptom deterioration (= delay of deterioration) might be of high importance. Also the longitudinal analysis looking at symptoms and HR QOL over time, at different visit intervals might be informative.

The compliance of the patients with the questionnaires should always be mentioned. One would like the compliance to remain through the study at $\geq 80\%$, in order to be able to analyse and interpret the results appropriately. In case of EORTC questionnaires, both EORTC QLQ LC 13 and QLQ C30 should be analysed to obtain a complete picture of not only lung cancer related symptoms, but also of symptoms related to cancer treatment toxicities.

The patient's symptoms are treated, especially the last months of life, by analgesics, cough suppressants, O₂, antidepressants, appetite stimulating agents and other supportive measures, which in final analysis, have to be incorporated. Other factors, such as performance status

(improving or deteriorating), weight loss and need for special emotional counselling are of great value in understanding the total value of lung cancer treatments.

CONCLUSION

In addition to efficacy and safety endpoints, PROs and HRQOL outcomes are important in patients in advanced NSCLC, when the data are collected and analysed correctly. They should be viewed as components of the total value of a treatment. They should provide, together with the other concern endpoints, a comprehensive picture of the benefits and risks of anticancer therapies. This position has been taken by Food and Drug Administration, (2003) and European Medicine Agency^[18,19].

To collect and analyse the PROs and HRQOL data with high quality, completeness and an excellent patient's compliance, a dedicated personnel is required. The process is time-consuming, it has to be a team work of knowledgeable, devoted workers, who are ready to participate in clinical trials and thus deliver reliable results of PROs and HR QOL questionnaires. Obtaining not only prolonged PFS, but enabling patients to feel during the last months of their lives more comfortable and independent, is a very important task in the treatment of advanced NSCLC.

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