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Symptoms and quality of life: important patient outcomes?

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Abstract

Non-small-cell lung cancer (NSCLC) is often associated with a range of debilitating disease-related symptoms, which can lead to diminished quality of life (QoL). The Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire has been validated as a reliable and sensitive means of assessing QoL domains that are relevant to patient outcomes and includes a Lung Cancer Subscale (LCS) designed to assess lung-based symptoms. Two phase II gefitinib ('Iressa', ZD1839) monotherapy trials, IDEAL 1 and 2, investigated the effect of gefitinib on a number of endpoints, including disease-related symptoms and QoL, in patients with refractory advanced NSCLC. Rapid symptom improvement (SI) lasting for at least one month was seen in >40% of patients receiving gefitinib 250 mg/day. SI was correlated with objective tumour response, improvement in performance status and median survival. Both SI and objective response were predictive of patient survival.

Keywords: Gefitinib; Iressa; ZD1839; Symptom improvement; Quality of life; Non-small-cell lung cancer; NSCLC; Epidermal growth factor receptor; EGFR

1. Introduction

Non-small-cell lung cancer (NSCLC) is often associated with a range of debilitating symptoms including specific pulmonary problems such as cough, breathlessness, and haemoptysis, and more general symptoms such as fatigue and weight loss. In addition to these disease-related symptoms, patients may also suffer increased anxiety and reduced mobility, all of which can lead to a reduction in their quality of life (QoL). Interestingly, only 22% of NSCLC patients who had already received platinum-based chemotherapy said they would choose chemotherapy over supportive care for a 3-month improvement in survival, while 68% would choose chemotherapy if it substantially reduced symptoms even without prolonging life [1].

As symptom improvement (SI) is clearly an important outcome of cancer treatment from the patients' perspective, it has been suggested that beneficial effects on disease-related symptoms, QoL or survival could be used to measure the efficacy of new cancer drugs, rather than more traditional measures such as objective tumour response. This is particularly relevant for the novel biologically targeted agents such as the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) gefitinib ('Iressa', ZD1839), which offers a proportion of patients dramatic benefits in terms of tumour shrinkage, and a wider group of patients benefits in terms of stable disease and symptom improvement. However, for improvements in symptoms and QoL to be used as a new measure of the efficacy of anticancer drugs, it is important to ensure that the tools used to assess them are rigorously validated and sensitive enough to detect changes in individual, yet important, aspects of QoL.

One such tool is the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire, which has been validated as a reliable and sensitive means of assessing QoL domains relevant to patient outcomes (Table 1) [2–4]. The FACT-L includes a Lung Cancer Subscale (LCS), designed to assess improvements in disease-related symptoms of lung cancer and consisting of seven questions asked *weekly* concerning shortness of breath, cough, tightness in chest, difficulty in breathing, loss of appetite, weight loss, and lack of clear thinking. Each of these items is rated by the patient on a scale of 0-4, giving

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Table 1
Areas covered by the 5 FACT-L components

	Functional well-being	Social well-being	Emotional well-being	Physical well-being	LCS
FACT-L	√	√	√	√	√
TOI	√	–	–	√	√
Questions (scored)	I am able to enjoy life	I feel distant from my friends	I feel sad	I have nausea	I have been short of breath
	I have accepted my illness	I get emotional support from my family	I feel nervous	I have a lack of energy	I am losing weight
	I am able to work (including at home)	I get support from my friends	I am losing hope in the fight against my illness	I feel sick	I have a good appetite
	My work (including work at home) is fulfilling	I am satisfied with family communication about my illness	I am satisfied with how I am coping with my illness	I am forced to spend time in bed	I have been coughing
	I am sleeping well	My family has accepted my illness	I worry about dying	I have pain	My thinking is clear
	I am enjoying the things I usually do for fun	I feel close to my partner (or the person who is my main support)	I worry that my condition will get worse	Because of my physical condition, I have trouble meeting the needs of my family	I feel tightness in my chest
	I am content with the quality of my life right now	I am satisfied with my sex life		I am bothered by the side-effects of treatment	Breathing is easy for me

FACT-L, Functional Assessment of Cancer Therapy-Lung; TOI, Trial Outcome Index; LCS, Lung Cancer Subscale.

an overall score between 0 (most symptomatic) and 28 (asymptomatic). A 2-3-point change in group mean LCS score is associated with change in Eastern Cooperative Oncology Group (ECOG) performance status, weight loss, objective tumour response and time to progression, and is therefore considered to be clinically meaningful [5]. As an additional measure of QoL, the Trial Outcome Index (TOI) has been derived from the FACT-L and is a measure of the more physical aspects of patient QoL shown to be sensitive to drug therapy (Table 1). The FACT-L and TOI scores are derived in a similar manner to the LCS scores; the highest attainable scores are 136 and 84, respectively.

2. Gefitinib monotherapy provides improvement in disease-related symptoms

Two phase II gefitinib monotherapy trials, IDEAL 1 and 2 ('Iressa' Dose Evaluation in Advanced Lung cancer), investigated the effect of gefitinib on disease-related symptoms and QoL in patients with pretreated advanced NSCLC, using a weekly LCS diary card and the FACT-L questionnaire (version 4) administered every 28 days. To minimise the risk of affecting this subjective measurement, patients filled in the forms without help from relatives or staff and did so before clinical assessment or hearing any news on their disease status. To decrease any potential placebo effects, a 4-6-week screening period allowed optimisation of pulmonary medication, patients had up to 4 LCS evaluations before the first post-baseline radiological assessment, and SI was defined as an increase in LCS score of at least 2 points that had to be maintained for at least 4 weeks.

2.1. Disease-related symptoms at baseline

The median baseline LCS scores for evaluable patients (baseline LCS score of $\leq$24) were 18.0 and 16.7 in IDEAL 1 and 2, respectively. At baseline, almost all patients in both trials exhibited at least one of the pulmonary symptoms from the LCS and around two-thirds of patients had severe (LCS score 0–1) pulmonary symptoms (Fig. 1). Furthermore, the majority of patients were symptomatic for loss of appetite (>80%), and weight loss and lack of clear thinking were each seen in over half the patients in these studies, demonstrating that the patient population in these studies was highly symptomatic (Fig. 1).

2.2. Symptom improvement

SI lasting at least 1 month was seen in >40% of symptomatic patients receiving gefitinib 250 mg/day in IDEAL 1 and 2 [6,7]. In addition, the median time to SI was rapid, occurring within 8–10 days. In both trials at 250 mg/day, a similar SI rate was seen when the 2-point criterion for SI was increased to 3 points (over 38%), and even applying a 4- or 5-point criterion gave SI rates of approximately 20%.

In both trials at 250 mg/day, substantial improvements from baseline were seen in each of the LCS item scores,

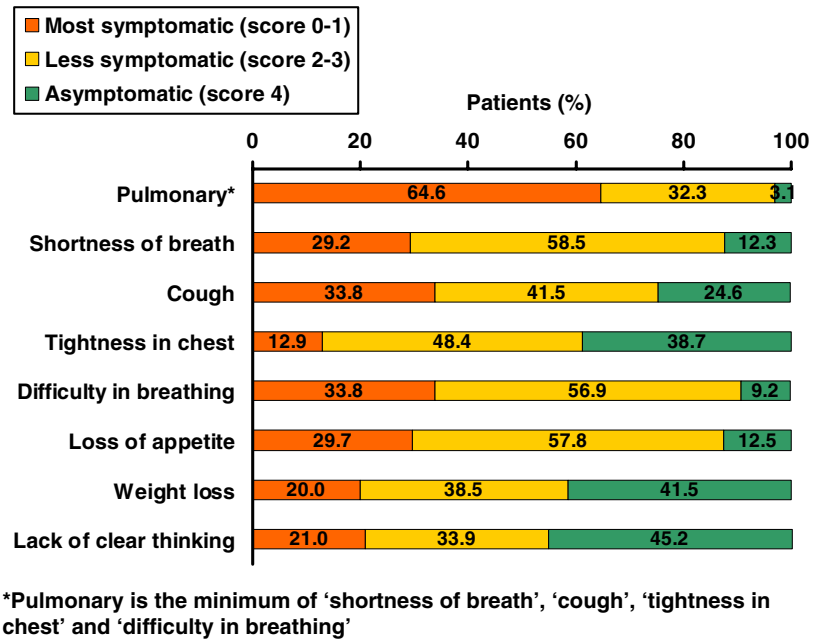

Fig. 1. LCS item score distribution at baseline in IDEAL 1, 250 mg/day. Reproduced with permission from: Douillard J-Y, Skarin A, Baselga J, *et al.* Improvement in disease-related symptoms and quality of life in patients with advanced non-small-cell lung cancer treated with ZD1839 ('Iressa') in IDEAL 1 and IDEAL 2. Poster presentation at ESMO, Nice, France, October 18–22, 2002 (poster 480).

particularly the pulmonary items and weight loss. Of the patients evaluable for improvement in each of the LCS items, almost all showed some improvement (at least 1 point at any time) in at least one of the pulmonary symptoms. Improvement in cough and tightness in chest was consistently high, seen in >89% of patients in both trials, while improvements in other LCS items were seen in the majority of patients (>75%).

Patient A was a 34-year-old man who was diagnosed with large-cell carcinoma of the lung with bone and brain metastases. Prior to his enrollment on the IDEAL 2 trial, he had completed a course of stereotactic radiotherapy, and failed two chemotherapy regimens. At trial entry, his LCS score was 24 and his WHO performance status was 0. Following treatment with 250 mg/day gefitinib, a partial tumour response was observed within 3 weeks. At week 4 his LCS score had improved to 28 (asymptomatic) and he reported being able to use an exercise bike for 30 minutes. At week 16 he reported running half a mile at least 3 times a week. At week 10 he developed acute bronchitis and his LCS score fell to 22; however, following resolution of the bronchitis, his LCS score recovered and was stable at the last recorded measurement at 24 weeks (Fig. 2). The patient's performance status has been stable since trial entry and his weight remained essentially unchanged. This case demonstrates that even small improvements on the LCS can have a large impact on the well-being of the patient.

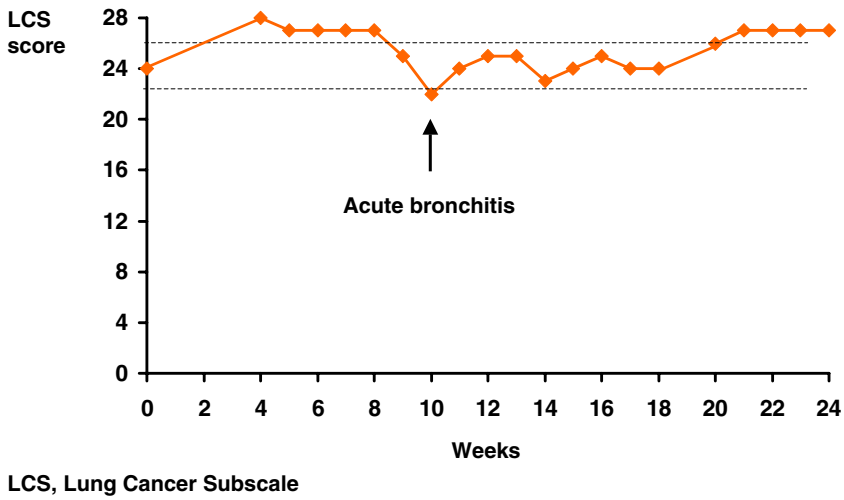

Fig. 2. Change in LCS score over time in Patient A.

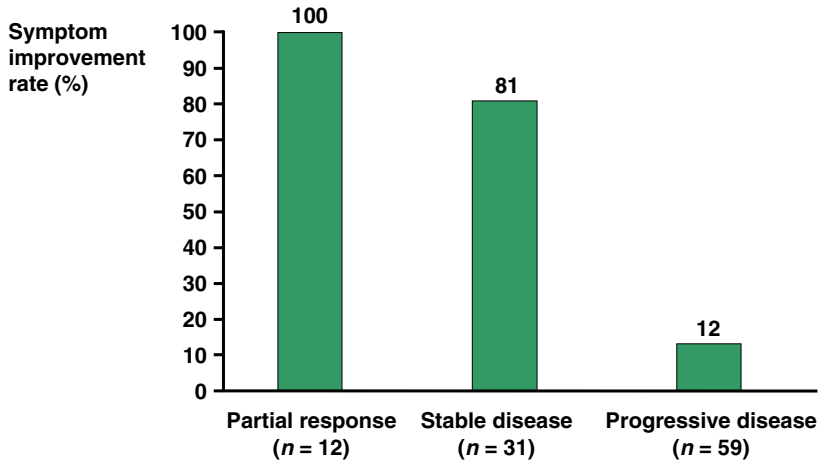

Fig. 3. SI benefits by tumour response in IDEAL 2, 250 mg/day. Reproduced with permission from: Cella D, Natale RB, Lynch TJ, *et al.* Disease-related symptoms in advanced non-small-cell lung cancer as measured by the Lung Cancer Subscale of the FACT-L questionnaire: clinically meaningful improvement with gefitinib ('Iressa', ZD1839). Poster presentation at ASCO, Chicago, IL, USA, May 31–June 3, 2003 (poster 2531). Reprinted with permission from the American Society of Clinical Oncology.

3. Symptom improvement is associated with tumour response and improvements in performance status

A positive correlation was observed between SI and objective tumour response in both trials with 250 mg/day gefitinib: the majority of patients (69.2-100%) with a partial response or stable disease showed SI, whereas only 12% of patients with progressive disease showed SI in either trial (Fig. 3) [8,9]. Furthermore, in IDEAL 2 the magnitude of improvement in LCS score also correlated with tumour response (Table 2).

Interestingly, there also appears to be a correlation between SI and improvements in performance status. In IDEAL 2 at 250 mg/day, performance status improvement was observed in 44% of evaluable patients with SI, while only 6% of patients without SI demonstrated improvements in performance status (AstraZeneca data on file).

4. Survival is associated with tumour response and symptom improvement

SI was also associated with increased overall survival. In IDEAL 1 and 2 at 250 mg/day, median survival was 13.3–13.6 months for patients with SI compared with 3.5–3.7 months for those without [10]. An analysis of the IDEAL 2 data demonstrated that median survival was longer in patients with SI and objective response than in those with SI but without objective response. Furthermore, median survival was longer in patients with stable disease and SI than in those with stable disease without SI (Fig. 4) [11].

Table 2
Mean LCS score improvements from baseline in IDEAL 2

Cohort	Improvement from baseline in mean LCS score (95% CI)
All patients	1.8 (1.2-2.4)
Partial response	4.8 (3.1-6.4)
Stable disease	2.6 (1.6-3.5)
Progressive disease	1.0 (0.2-1.9)

LCS, Lung Cancer Subscale; CI, confidence interval.

5. Gefitinib monotherapy provides improvement in quality of life

Patient populations in both trials had compromised QoL at entry, as measured using the FACT-L and TOI. Following treatment with 250 mg/day gefitinib, QoL improved in 23.9 and 34.3% of patients, as measured by FACT-L, and in 20.9 and 33.3% of patients, as measured by TOI, in IDEAL 1 and 2, respectively.

As with SI, patients who demonstrated an objective tumour response were more likely to have improvements in QoL (FACT-L) than those who did not. For the evaluable patients with an objective tumour response, the FACT-L improvement rate was 53.8 and 91.7%, while 40.0 and 61.3% of patients with stable disease had improvements in FACT-L and only 2.9 and 8.4% of patients with progressive disease reported an improvement in FACT-L in IDEAL 1 and 2, respectively. Similar results were seen for TOI.

Patient B, a 56-year-old woman, entered IDEAL 2 with stage IV adenocarcinoma of the lung with liver and bone metastases. She had rapidly progressive disease despite three chemotherapy regimens over an eight-month period and two courses of radiation (to the left ribs and the lumbar-sacral spine). At trial entry she had severely impaired QoL (FACT-L, 56; TOI, 27) and was confined to a wheelchair. One month after the start of gefitinib therapy (250 mg/day) her FACT-L and TOI scores had

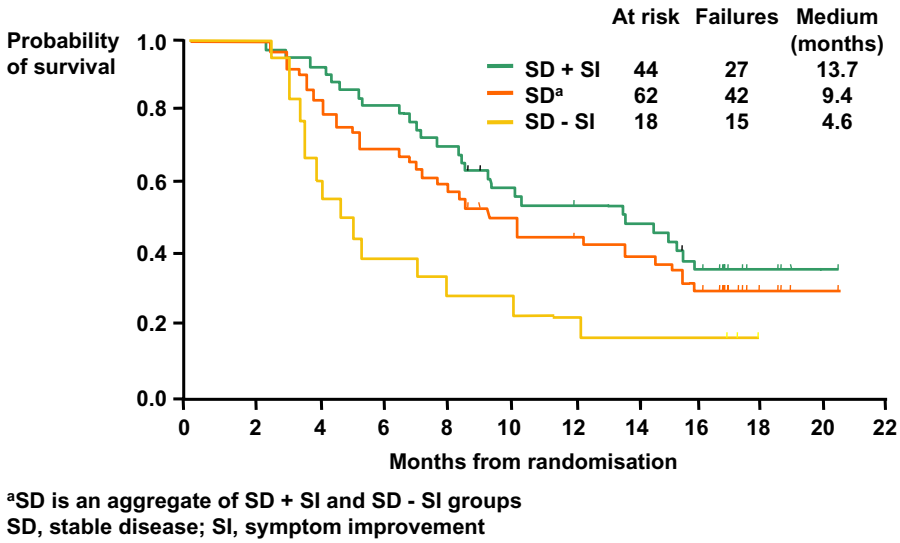

Fig. 4. Overall survival in the subset of patients surviving for >8 weeks with stable disease, with or without SI, IDEAL 2. Reproduced with permission from: Cella D, Natale RB, Lynch TJ, *et al.* Disease-related symptoms in advanced non-small-cell lung cancer as measured by the Lung Cancer Subscale of the FACT-L questionnaire: clinically meaningful improvement with gefitinib ('Iressa', ZD1839). Poster presentation at ASCO, Chicago, IL, USA, May 31–June 3, 2003 (poster 2531). Reprinted with permission from the American Society of Clinical Oncology.

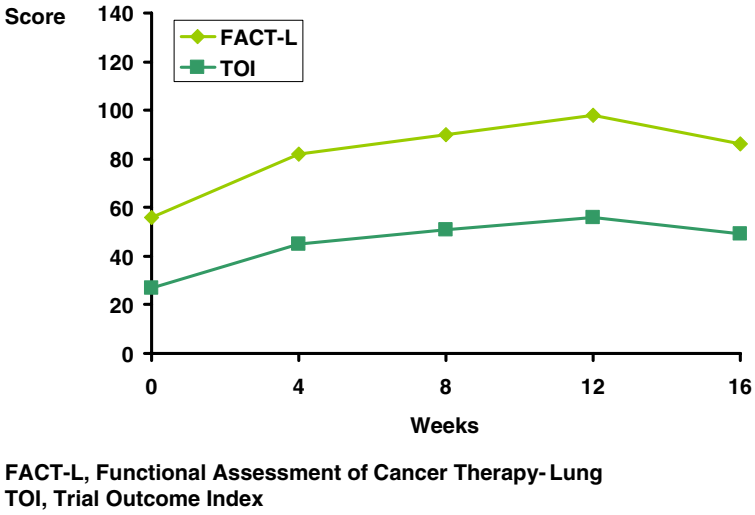

Fig. 5. Change in FACT-L and TOI score over time in Patient B.

improved to 82 and 45, respectively. This improvement was sustained for at least 15 weeks (Fig. 5), at which time the patient was able to walk with assistance. Her WHO performance status improved from 2 to 1 at week 5 and remained stable, and her weight remained essentially unchanged. A partial tumour response was seen at week 12 and was ongoing at week 21.

6. Conclusions

Improvements in disease-related symptoms and QoL are key desired outcomes of NSCLC treatment and should, therefore, be included as endpoints of clinical trials assessing new therapies for advanced NSCLC. Furthermore, improvements in disease-related symptoms and QoL are associated with other clinical benefits, such as tumour response, improvements in performance status and survival. In phase II trials, gefitinib produced substantial improvements in disease-related symptoms and QoL in patients with advanced NSCLC.

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