J Cancer Res Clin Oncol (2005) 131: 783–788
DOI 10.1007/s00432-005-0029-9

ORIGINAL PAPER

**Alain Gelibter · Anna Ceribelli · Camillo F. Pollera
Michele Milella · Luca Moscetti · Isabella Sperduti
Francesco Cognetti**

Impact of gefitinib ('Iressa') treatment on the quality of life of patients with advanced non-small-cell lung cancer

Received: 2 May 2005 / Accepted: 26 July 2005 / Published online: 24 September 2005

Abstract *Purpose:* Patients with advanced non-small-cell lung cancer (NSCLC) have a short life expectancy; therefore, in addition to increasing their survival, improving their quality of life (QoL) is also an important treatment goal. *Methods:* We evaluated the QoL of patients with advanced NSCLC who were unfit to receive chemotherapy, failed to respond or progress following prior chemotherapy, who received subsequent treatment with gefitinib ('Iressa') on a compassionate use basis, using a standard QoL questionnaire, (EORTC) QLQ-C30 and the related lung cancer-specific module QLQ-LC13. *Results:* Analysis of the functional scales showed a trend towards improvement for role, emotional and cognitive scales, while a substantial stability was seen for general QoL scale. Analysis of the symptoms scales of QLQ-C30, showed a trend towards improvement for fatigue, dyspnoea, insomnia, and constipation, after one month of therapy. Fifty-six of the 57 patients were considered evaluable for response. One patient evidenced a partial response (patient is still on response), 29 patients had stable disease for a median duration of 5months (range 4–7 months), and 26 patients progressed. *Conclusions:* After treatment with Gefitinib, we observed maintenance of QoL in a group of patients with poor prognosis that would be expected to have a worsening QoL. Furthermore important symptoms like dyspnoea fatigue and pain in other parts, that usually afflict patients with NSCLC, showed a trend toward improvement after only one month of therapy.

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A. Gelibter (✉) · A. Ceribelli · M. Milella · I. Sperduti
F. Cognetti
Division of Medical Oncology A, Regina Elena Cancer Institute,
Via Elio Chianesi, 53, Rome 00144, Italy
E-mail: agelibter@yahoo.it
Tel.: +39-06-52666919
Fax: +39-06-52665637

C. F. Pollera · L. Moscetti
Medical Oncology, Belcolle Hospital, Viterbo, Italy

Keywords Quality of life · Gefitinib ('Iressa') · Non-small-cell lung cancer

Introduction

Patients with advanced non-small-cell lung cancer (NSCLC) have a short life expectancy; therefore, in addition to increasing their survival, improving their quality of life (QoL) is also an important treatment goal. Assessment scales in the form of questionnaires have been developed to objectively evaluate and quantify NSCLC-related symptoms and QoL parameters. In clinical trials of patients with advanced NSCLC, these questionnaires can assess changes in NSCLC-related symptoms and QoL while patients are receiving treatment, which can be quantified and related to clinical end points such as tumour response and survival. Current chemotherapy and/or radiation regimens may offer some symptom relief, although they are often associated with significant toxicity, and hence may actually impair QoL. In contrast, novel targeted therapies, which have a more favourable tolerability profile than chemotherapy, have the potential to improve both tumor response and QoL (Natale and Zaretsky 2002) In this context, we evaluated the QoL of patients with advanced NSCLC who were unfit to receive chemotherapy, failed to respond or progressed following prior chemotherapy; who received subsequent treatment with gefitinib ('Iressa') on a compassionate use basis, using a standard QoL questionnaire, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and the related lung cancer-specific module QLQ-LC13.

Materials and methods

Patient eligibility criteria

Patient eligibility criteria for this analysis were as follows: age >18 years; histologically or cytologically

confirmed NSCLC; inoperable stage IIIB or IV disease, or relapsed unresectable disease; ECOG performance status 0–3; adequate bone marrow, liver and renal functions. Patients were eligible if they had received prior surgery or radiotherapy, and previous chemotherapy, or were unfit to receive chemotherapy. At least one indicator lesion (according to World Health Organization [WHO] criteria) measurable by computed tomography (CT) scan and $>20\times10$ mm was mandatory. Exclusion criteria were as follows: pregnant/lactating women or those of child-bearing potential who were not using effective contraception; concomitant treatment with any other anticancer agents; psychologic, familial, sociologic or geographic problems. The analysis was conducted in accordance with the ethical principles set out in the Declaration of Helsinki (Somerset West amendment) and was approved by the ethics committees of the Regina Elena Cancer Institute. All patients who entered this series gave written informed consent according to the requirements of the national legislation of the country.

Treatment

Oral gefitinib at the dose of 250 mg/day was administered until progression of disease, unacceptable toxicity or patient refusal.

Quality of life (QoL)

Quality of life (QoL) assessments, based on the EORTC QLQ-C30 (version 3.0) and QLQ-LC13 questionnaires, were performed before entry and before monthly visit, and data were analyzed according to the Guidelines of the Quality of Life Committee of the National Cancer Institute of Canada Cancer Treatment Group (Aaronson et al. 1993; Bergman et al. 1994) . Patients were evaluable for QoL if they had completed both a baseline questionnaire and a questionnaire after one month of therapy with Iressa.

The core questionnaire EORTC QLQ-C30 is a 30-item questionnaire composed of five multi-item functional subscales: physical, role, emotional, social, and cognitive functioning; three multi-item symptom scales measuring fatigue, pain, and emesis; a global health status and QoL subscale; and six single items to assess financial impact and symptoms such as dyspnea, sleep disturbance, appetite, diarrhea, and constipation. The 13-item lung cancer-specific module comprises both multi- and single-item measures of lung cancer-associated symptoms (e.g. coughing, hemoptysis, dyspnea, pain) and side-effects from conventional chemotherapy and radiotherapy (e.g. hair loss, neuropathy, sore mouth, dysphagia). Both questionnaires are designed to be completed by the patient.

Multi-item scales are computed by calculating the mean raw scores of single items and transforming them linearly so that all scales range from 0 to 100. For single items, only linear transformation is performed. For functional scales (i.e., those exploring physical, role, emotional, social and cognitive functioning and global health status), a higher value indicates a better level of function; for symptoms scales and items, a higher value indicates increased severity of symptoms.

Comparison of scores of global health status at baseline, and at the end of the first month of treatment was the primary consideration of this analysis. Scores were compared by Wilcoxon rank sum test. Changes from baseline were calculated at each time point for each domain or symptom and a change in score of ≥10 points from baseline was defined as clinically relevant (Osoba et al. 1998). Computationally, an ordinary binary logistic model was fitted after the data matrix was restructured in a convenient way (Armstrong and Sloan 1989; Berridge and Whitehead 1991) [8,9] using SSPI software

Tolerability and efficacy assessments

Adverse events (classified by NCI-CTCAE version 3.0) experienced by each patient were recorded throughout the treatment.

Pre-treatment evaluation consisted of physical examination, complete blood count, biochemical screen, chest X-ray, and CT of the chest, brain and abdomen. Other imaging procedures were performed, if clinically indicated. Hematologic and biochemical monitoring was performed monthly. All imaging procedures were repeated every 3 months.

Tumor response was assessed according to WHO criteria (WHO 1979) with EORTC modifications (Therasse et al. 2000) Objective responses were evaluated at the end of the third month of treatment by repeating staging procedures. The best response was recorded for each patient. For clinically evident or suspected progression of the disease, response evaluation was anticipated. Confirmation of response after 1 month was not performed. Patients who stopped treatment because of toxicity or refusal before restaging were defined as non-responders in the calculation of response rate. The objective response rate was defined as the proportion of complete and partial responses compared with the total number of patients.

Time to progression was defined as the interval from the date of starting treatment to the date of progression or death (whichever occurred first). Patients who died before completion of restaging procedures were defined as having progressed on the date of death. Overall survival was defined as the interval from the date of starting treatment to the date of death. Patients without documented objective progression or death at the time of the final analysis were censored at the date of their last objective tumor assessment or the date last known to be alive, respectively. Time-to-event curves were estimated by the Kaplan-Meier product limit method (Kaplan and Meier 1958).

Analyses of time to progression, survival (median and 1-year) and tolerability were performed on an intention-to-treat basis.

Results

Patient characteristics

From October 2001 to July 2003, 57 patients with NSCLC were enrolled in this multi-center trial (Table 1), of whom 40 were male. Patient ages ranged from 36 to 79 years (median age 62 years) and 63 and 37% of patients had PS score of 0–1 and 2–3, respectively. Almost all patients (93%) had metastatic disease at entry and the majority (67%) presented with adenocarcinoma. One patient received Gefitinib as first-line treatment due to comorbidities present in medical history, and 28, 26 and 2 patients, respectively received Gefitinib as second, third and fourth line treatment.

Table 1 Demography

Patients, **n**	57
Evaluable for response	56
Evaluable for QoL	57
Male : female, **n**	40:17
Median age (range), years	62 (36–79)
Performance status, **n**	
0	10
1	26
2	20
3	1
Disease stage, **n**	
Locally advanced	4
Metastatic	53
Histology, **n**	
Adenocarcinoma	38
Squamous cell carcinoma	4
Undifferentiated/poorly differentiated	14
Broncho-alveolar carcinoma	1
Line of treatment, **n**	
First	1
Second	28
Third	26
Fourth	2

Quality of life

Fifty-seven patients completed the QoL questionnaires. Trends of all the items from QLQ-C30 at baseline and at the first evaluation are shown in Fig. 1a, b. Analysis of the functional scales (Figure 1a) showed a trend towards improvement for role, emotional and cognitive scales, while a substantial stability was seen for general QoL scale. Analysis of the symptoms scales of QLQ-C30 (Fig. 2b), for which a decrease from baseline corresponded to an improvement, showed a trend towards improvement for fatigue, dyspnoea, insomnia, and constipation, after 1 month of therapy. A stability were seen for nausea/vomiting, pain, appetite loss, and financial. As expected, a worsening was seen for diarrhea.

Analysis of the symptoms from the QLQ-LC13 questionnaire is shown in Fig. 2. A trend towards improvement (i.e. decreases from baseline) was seen for dyspnea, peripheral neuropathy, alopecia and pain in other parts. A stabilization was observed for cough, hemoptysis dysphagia, pain in arm or shoulder, whereas sore mouth and chest-pain became relatively worse (i.e. increased from baseline).

Tolerability

No hematologic toxicity greater than grade 1 was recorded, and these cases are probably correlated with previous chemotherapy treatments. Twenty-seven patients had skin rash (grade 1 in 24, grade 2 in 3 and one grade 3). Two patients discontinued treatment for 1 week due to grade 2 skin rash and subsequently restarted gefitinib without further problems. Six patients experienced grade 1 diarrhea, and only one patient had grade 3 diarrhea which resolved after treatment discontinuation for 1 week. No patient indefinitely discontinued treatment due to any toxicity. No drug-related interstitial lung disease was observed. No other grade 3/4 treatment-related adverse events were observed.

Efficacy

Fifty-six of the 57 patients were considered evaluable for response. One patient experienced a partial response (patient is still on response), 29 patients had stable disease for a median duration of 5 months (range 4–7 months), and 26 patients progressed. One patient is lost to follow-up.

The median time to progression was 3 months (95% CI 2–4.2 months), the median overall survival was 6 months (95% CI: 4.3–7.1) (Fig. 3), and 1-year survival rate was 21%.

Discussion

The outcome of patients with NSCLC failing or progressing after first-line chemotherapy was poor. Two randomized trials demonstrated the advantage of docetaxel over either vinorelbine or ifosfamide (Fossella et al. 2000) and over best supportive care in this setting (Shepherd et al. 2000). However, the overall response rate after docetaxel 75 mg/m^2 was only 5.5–6.7%. Despite this low response rate, treatment with docetaxel resulted in a significant prolongation of median survival versus best supportive care. Median survival in these two trials ranged from 5.7–7.5 months, with 1-year survivals

of 32–37% when this drug was given at a dose of 75 mg/m^2 every 3 weeks (Fossella et al. 2000; Shepherd et al. 2000). Following these trials, docetaxel at 75 mg/m^2 every 3 weeks has been considered as the gold standard for patients with NSCLC who have previously been treated with a first-line platinum-based regimen. Taking into consideration these dismal results, and the fact that this population has terminal disease, goals of treatment should include palliation, acceptable QoL and symptom improvement, together with prolongation of survival. QoL data from the randomized trial of docetaxel versus best supportive care showed a trend towards less deterioration in QoL with docetaxel (Dancey et al. 2004).

Health-related QOL has been recommended as one of the end-points for clinical cancer research (Montazeri et al. 2001). Use of QOL instruments may be particularly appropriate when treatments are not expected to achieve significant advantages in terms of overall survival: in the case of metastatic cancer, guidelines from the American Society of Clinical Oncology state that a treatment can be recommended even without an improvement in survival, if it demonstrates an improvement in terms of QoL (American Society of Clinical Oncology 1996). Treatment of pretreated NSCLC patients represents one such case.

In addition, it should not be forgotten that patients might have a preference for a treatment potentially able to improve their QoL rather than their survival. A US study showed that of patients who had previously received cisplatin, only 22% of patients would choose chemotherapy over best supportive care for a 3-month improvement in survival (Silvestri et al. 1998). Conversely, 68% patients would choose chemotherapy if it substantially reduced symptoms, even with no prolongation of life. A good QoL should be a primary goal in the treatment of patients with NSCLC who have already received one or two lines of chemotherapy, but to-date very few studies have specifically focused on this topic.

Response rate may not be the most appropriate end-point when evaluating targeted agents such as gefitinib, as these agents act primarily by inhibiting tumour cell proliferation, in contrast to cytotoxic agents (Rowinsky 2001). Due to this mechanism of action, disease control rate may better reflect the positive effect of targeted agents on the patient. In this series of patients, a disease control rate of approximately 53% was achieved.

Other major outcomes included a median time to progression of 3 months (95% CI 2–4.2 months), a median survival of 6 months (95% CI: 4.3–7.1) and a 1-year survival probability of 21%. These results are similar to those from Phase II trials of gefitinib monotherapy ('Iressa' Dose Evaluation in Advanced Lung cancer [IDEAL] trials) in patients with advanced NSCLC refractory to prior chemotherapy (Fukuoka et al. 2003; Kris et al. 2003), highlighting that data from real-life use of gefitinib support the favourable results seen in the trial setting.

In our analysis of QoL with gefitinib we observed maintenance of QoL in a group of patients with poor prognosis that would be expected to have a worsening QoL. Furthermore important symptoms like dyspnoea fatigue and pain in other parts, that usually afflict patients with NSCLC, showed a trend toward improvement after only one months of therapy.

QoL and symptom improvement were also assessed in the gefitinib Phase II IDEAL trials. These analyses used a different QoL instrument, the Functional Assessment of Cancer Therapy - Lung (FACT-L), incorporating the Lung Cancer Subscale (LCS) which evaluates disease-related symptoms. For patients

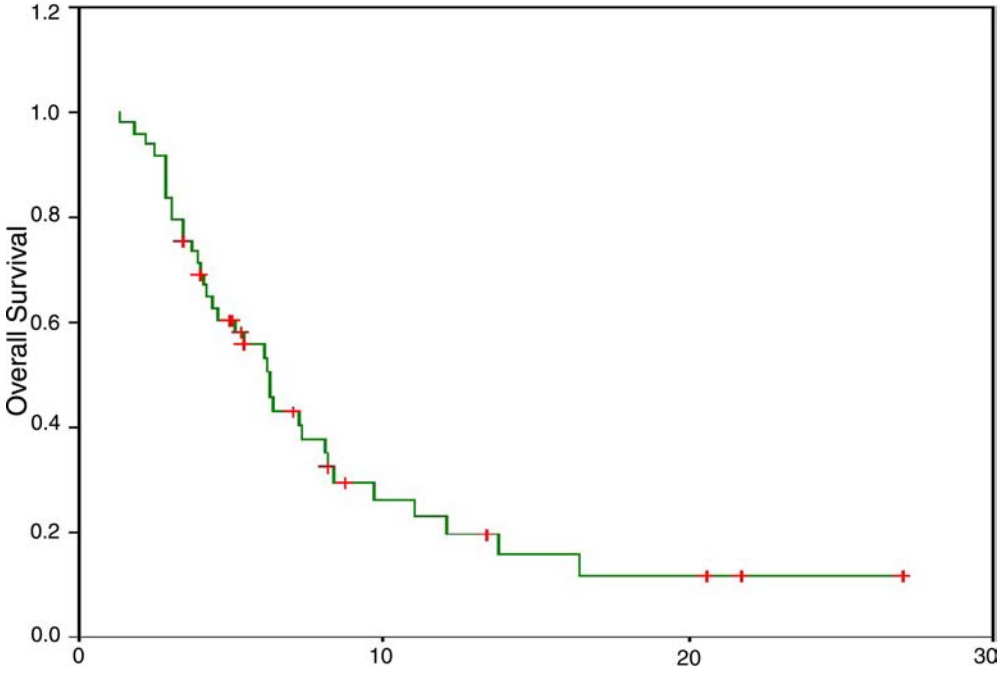
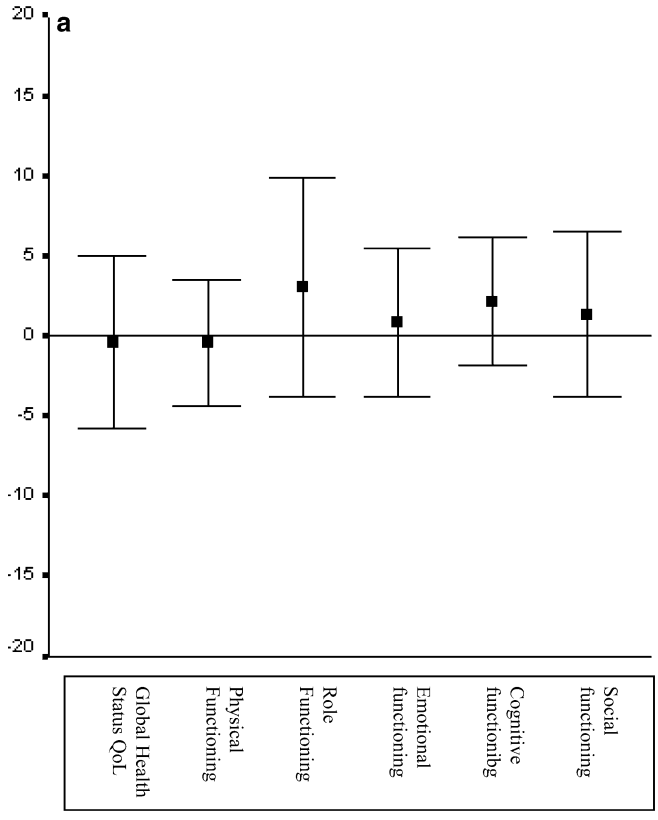


Fig. 1 Kaplan Meier estimate of overall survival



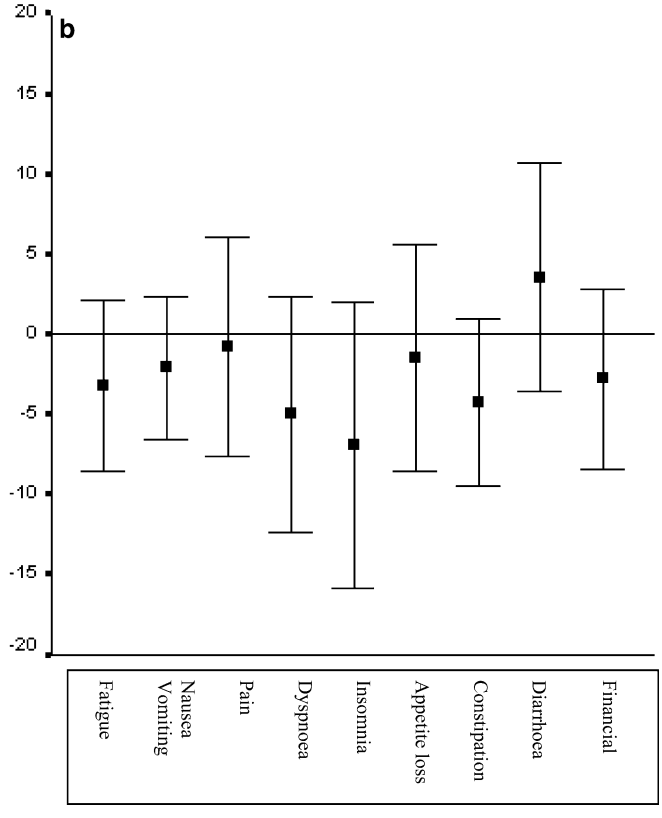


Fig. 2 Change from baseline for items of QLQ-C30, where improvement is represented by a positive change from baseline for **a** functional items and a negative change from baseline for **b** symptom items

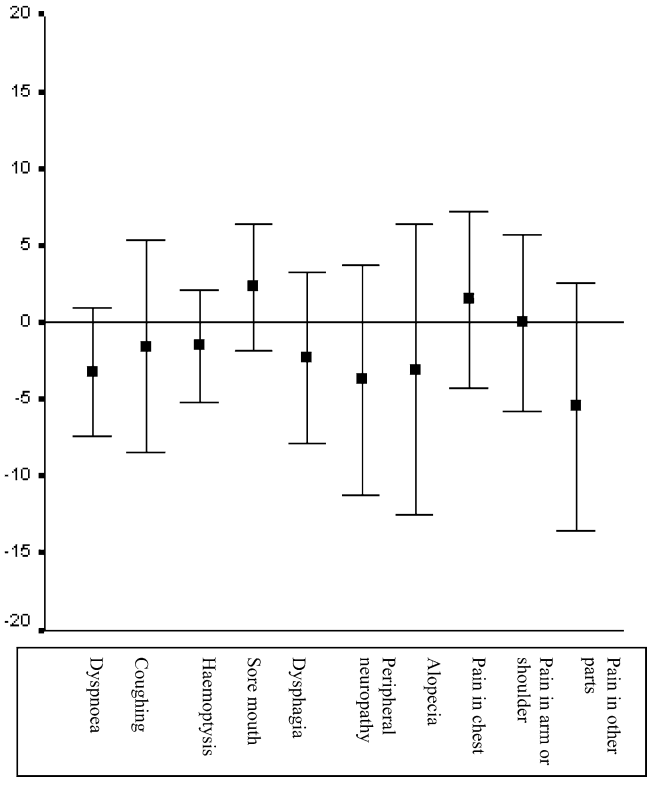


Fig. 3 Change from baseline for items of QLQ-LC13

receiving gefitinib 250 mg/day, improvements in QoL and in symptoms were observed in >20% and approximately 40% of patients, respectively (Douillard et al. 2002; Natale et al. 2002).

In conclusion, some steps have been taken in the field of clinical cancer research dedicated to NSCLC patients treated with targeted therapies. In addition to assessing improvements in overall survival, we should be aiming to enhance the role of QoL assessment in this patient population. Refractory advanced NSCLC is often associated with declining QoL and short survival time; therefore, even modest improvements (or stabilization) of QoL may be worthwhile for these patients.

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