Symptom Improvement in Lung Cancer Patients Treated With Erlotinib: Quality of Life Analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21

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ABSTRACT

Purpose
This report describes the quality of life (QOL) findings of a randomized placebo controlled study of erlotinib, an epidermal growth factor receptor inhibitor, in patients with non–small-cell lung cancer (NSCLC).

Patients and Methods
This double-blind phase III trial randomly assigned 731 patients with NSCLC who had progressed after prior chemotherapy to erlotinib 150 mg daily or placebo, with survival as the primary study outcome. QOL was assessed by European Organisation for Research and Treatment of Cancer QLQ-C30 and the lung cancer module QLQ-LC13. The primary end points for QOL analysis were time to deterioration of three common lung cancer symptoms: cough, dyspnea, and pain.

Results
Survival was significantly longer (hazard ratio, 0.70; \(P < .0001\)) in the erlotinib arm. Compliance with QOL was 87% at baseline and more than 70% during treatment. Patients receiving erlotinib had significantly longer median time to deterioration for all three symptoms (4.9 v 3.7 months for cough \(P = .04\); 4.7 v 2.9 months for dyspnea \(P = .04\), and 2.8 v 1.9 months for pain \(P = .03\)). QOL response analyses showed that 44%, 34%, and 42% of patients receiving erlotinib had improvement in these three symptoms, respectively. This was accompanied by a significant improvement in the physical function (31% erlotinib v 19% placebo, \(P = .01\), and global QOL (35% v 26%, \(P < .0001\)). Patients with complete or partial response were more likely to have improvement in the QOL response than patients with stable or progressive disease (\(P < .01\)).

Conclusion
Erlotinib not only improves survival in previously treated patients with NSCLC, but also improves tumor-related symptoms and important aspects of QOL.

INTRODUCTION

Lung cancer continues to be a leading cause of cancer death; despite improved outcomes with early-stage and locally advanced non–small-cell lung cancer (NSCLC), most patients present with incurable disease. Chemotherapy as first-line and second-line treatment prolongs survival, and improves symptoms and quality of life (QOL). However, third-line chemotherapy has shown less benefit. Molecularly targeted agents are promising agents. Erlotinib, a tyrosine kinase epidermal growth factor receptor inhibitor, prolonged survival compared with placebo in the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) study BR.21. Detailed symptom and QOL analyses, an integral part of that study, are reported herein.

PATIENTS AND METHODS

This phase III trial was coordinated by NCIC CTG, supported by funding from the NCIC, the Canadian Cancer Society, and OSI Pharmaceuticals Inc (Melville, NY). NCIC CTG maintained the trial database and conducted all analyses.

Patients
Eligible patients had to have performance status 0 to 3, proof of NSCLC, and prior treatment with one or two
chemotherapy regimens. Details of the patient eligibility have been reported previously. Participating institutions received approval from their institutional ethics review boards; all patients provided written informed consent and had to complete QOL questionnaires.

**Study Procedures**

After baseline assessment, patients were randomly assigned in a 2:1 ratio to receive erlotinib 150 mg orally daily or placebo, until disease progression or unacceptable toxicity. Primary study end point was overall survival (OS). Secondary end points included progression-free survival, response rate, duration of response, toxicity, and QOL.

**QOL Assessment**

The European Organisation for Research and Treatment of Cancer (EORTC) QOL questionnaire (QLQ-C30) and the EORTC QLQ-LC13 lung module were used to assess QOL at baseline and every 4 weeks during treatment, 4 weeks after completing treatment, and every 12 weeks thereafter until documentation of progressive disease. The EORTC QLQ-C30 is a self-administered, cancer-specific questionnaire with multidimensional scales; it consists of five functional domains (physical, role, emotional, cognitive, and social); three symptom domains (fatigue, nausea/vomiting, and pain); six single items (dyspnea, sleep, appetite, constipation, diarrhea, and financial impact) and a global QOL domain. The EORTC LC13 module addresses specific issues in lung cancer patients that may not be addressed adequately by the core questionnaire. The module comprises 13 questions incorporated into one multi-item scale designed to evaluate dyspnea and a series of single items assessing different types of pain, as well as cough, hemoptysis, dysphagia, sore mouth, alopecia, and peripheral neuropathy. For each domain and item, a linear transformation is applied to standardize the raw score to a range from 0 to 100, with 100 representing best possible function/QOL, and highest burden of symptoms for symptom domains and single items.

Patients from all countries were expected to complete QOL questionnaires, with the exception of Thailand (for any QOL assessments), and Romania and Brazil (for lung cancer module completion), since those questionnaires were not available in the local language; those patients are excluded from the calculation of compliance rates. Translations of the core questionnaire and/or lung module were previously performed and validated, according to the standard EORTC procedures.

**Statistical Considerations**

The trial was designed to detect, with 90% power using a two-sided 5% level test, 33% improvement in median survival from an estimated 4 months for patients receiving placebo. The primary end point in the QOL analysis was defined prospectively as the time from random assignment to deterioration in the following three common lung cancer symptoms: cough (Question 1 in QLQ-LC13), dyspnea (Question 8 in QLQ C30), and pain (Questions 9 and 19 in QLQ C30). These symptoms were selected during accrual to the study, before any analyses, as clinically relevant and frequently present in patients with advanced NSCLC. Patients were considered as deteriorated for a given symptom if their change score from baseline was 10 points or higher at any time without any improvement. Patients who had less than 10-point changes from baseline at every QOL assessment were considered as stable. Classification into improved/worsened categories was reversed for symptom domains and single items because a positive change indicates worsening (ie, more symptoms). \( \chi^2 \) test was used to compare the distributions of these three categories between two arms; for the scale/domains with statistically significant differences between the arms, the logistic regression model with the aforementioned covariates was used to identify factors predictive of improvement or worsening. For global QOL, physical functioning, cough, dyspnea, and pain, the correlation between QOL response and objective tumor response was evaluated by \( \chi^2 \) test for all patients for whom those data were available.

### RESULTS

**Patient Characteristics**

Seven hundred thirty-one patients were accrued onto BR.21 from 15 countries (488 receiving erlotinib and 243 in the placebo arm). There were no apparent imbalances in the patient characteristics between the arms: median age was 61 years, 65% of patients were male, 50% had adenocarcinoma, and performance status was predominantly 0 or 1.

**Summary of Clinical Outcomes**

Patients in the erlotinib arm had a response rate of 8.9% (median duration of response, 7.9 months), and a significant prolongation of progression-free survival (2.2 versus 1.8 months; hazard ratio [HR], 0.61; \( P < .0001 \)) and OS (6.7 versus 4.7 months; HR, 0.70; \( P < .0001 \)). One-year survival was 31% in the erlotinib arm, versus 22% in the placebo arm.

**QOL Compliance**

Compliance with QOL assessment is summarized in Table 1: 425 (93.0%) of 457 of patients randomly assigned to erlotinib and eligible for QOL completed the baseline QOL assessment, compared with 213 (93.8%) of 227 patients on placebo. Compliance rates, as expressed by percentage of eligible patients who were expected to complete QOL questionnaires at a certain time point (ie, they had neither died nor progressed), were in the 65% to 90% range while on treatment; this represented smaller numbers of patients as time progressed.

**Baseline QOL Results**

The two study arms had similar baseline QOL scores in all domains and items (Fig 1). The greatest impairment was seen in global QOL (mean scores, 55.3 and 53.5 in the erlotinib and placebo arms, respectively), role functioning (mean, 58.9 and 60.0) and physical functioning (mean, 65.4 and 64.4). Symptoms with the highest mean baseline scores were fatigue (mean, 42.5 and 45.4, respectively), pain (mean, 34.2 and 38.3), cough (mean, 43.4 and 39.0), and dyspnea (mean, 31.9 and 33.5).
Primary QOL Analysis: Response of Main Lung Cancer Symptoms

Figure 2 summarizes the time to deterioration of the three main lung cancer symptoms. The median time to deterioration of cough was 4.9 months (95% CI, 3.8 to 7.4 months) for patients receiving erlotinib, and 3.7 months (95% CI, 2.0 to 4.9) for patients receiving placebo (Hochberg adjusted \( P = .04 \); Fig 2A). Median time to deterioration of dyspnea was 4.7 months (95% CI, 3.8 to 6.2 months) and 2.9 months (95% CI, 2.0 to 4.8 months), respectively (adjusted \( P = .03 \); Fig 2B); and of pain 2.8 months (95% CI, 2.4 to 3.0 months) and 1.9 months (95% CI, 1.8 to 2.8 months), respectively (adjusted \( P = .04 \); Fig 2C). Cox regression analyses showed that, besides treatment with erlotinib (\( P = .04 \) for cough; \( .004 \) for dyspnea; \( .02 \) for pain), the following factors were associated with longer time to deterioration of symptoms: for cough, never having smoked (\( P = .02 \)); for dyspnea, performance status of 0 or 1 (\( P = .002 \)) and stable disease after prior therapy (\( P = .01 \)); and for pain, stable disease after prior therapy (\( P = .001 \)).

Secondary QOL Analysis: Proportion of Patients Improved/Stable/Worse

Table 2 details the QOL responses for all of the main QOL domains, global QOL, and single items of the core questionnaire and lung cancer module. Statistically significant differences favoring erlotinib were seen for physical functioning, pain, cough, dyspnea, and constipation. Multivariate logistic analyses showed that treatment with erlotinib (\( P = .006 \)) and performance status of 0 or 1 (\( P = .045 \)) were independent predictors for pain; treatment with erlotinib (\( P = .004 \)), never having smoked (\( P = .003 \)), and performance status of 0 or 1 (\( P = .02 \)) were predictors for cough; and treatment with erlotinib (\( P = .01 \)) and more than one prior regimen (\( P = .02 \)) were predictors for dyspnea. Female sex (\( P = .01 \)) was the only independent predictor for improvement in constipation. Significantly more patients receiving erlotinib worsened, and fewer patients on placebo had improvement in diarrhea. Multivariate logistic analyses identified treatment with erlotinib (\( P < .0001 \)), performance status 0 or 1 (\( P = .02 \)), never having smoked (\( P = .02 \)), female sex (\( P = .045 \)), and adenocarcinoma (\( P = .007 \)) as independent predictors for worsening diarrhea. Some domains and items had more patients treated with erlotinib in both improved and worsened categories. By grouping three categories into two (improved and not improved; worsened and not worsened) based on the category (improved or worsened) with larger difference between two treatment groups, we found that significantly more patients treated with erlotinib improved in global QOL (\( P = .04 \)) and emotional functioning (\( P = .04 \)) and worsened in sore mouth (\( P < .0001 \)) and hair loss (\( P < .0001 \)). Multivariate analyses identified that treatment with erlotinib (\( P = .045 \)) and stable disease after prior therapy (\( P = .02 \)) were independent predictors for improvement in global QOL. No predictor for improvement in emotional functioning was found from these multivariate analyses.

Correlation Between QOL Response and Objective Tumor Response

Table 3 lists the distribution of number and percentage of patients who had improvement in global QOL, physical functioning, cough, pain, and dyspnea, across three objective tumor response categories. For all the QOL scale and domains analyzed, patients with complete remission/partial remission were more likely to have improvement in the QOL response than patients with either stable or progressive disease.
DISCUSSION

This large, randomized study of erlotinib versus placebo as second- or third-line treatment in NSCLC has demonstrated a survival benefit and a statistically and clinically significantly longer time to deterioration of thoracic symptoms and improvements in global QOL and physical functioning on the erlotinib arm that was correlated with response to erlotinib. The efficacy of chemotherapy in incurable malignancies is usually assessed through response rates, toxicity, disease-free survival, and OS. However, these parameters do not allow for an assessment of the overall therapeutic benefit because they do not provide information about the clinical condition of the patients, their experience while undergoing treatment, or the quality of their survival. Treatment choices that patients make are influenced by numerous factors, including the value they place on potential improvements in survival. Studies have shown that cancer patients want to have QOL information to help in their decision making, and that most oncologists are unwilling to prolong survival at the expense of worsening QOL, although QOL considerations play a relatively small role in treatment decisions in current practice.

Toxicity reporting could be seen as an indirect indicator of QOL, and if toxicity is mild, prolonged survival time can be assumed to be of good quality. However, biochemical and laboratory changes may not have a direct impact on the patient. Moreover, critical examination of the validity and reliability of toxicity reporting reveals under-reporting and significant intraobserver variability. Studies that have compared QOL with toxicity reporting demonstrate lower rates of reporting by study personnel for symptoms such as fatigue, dyspnea, and pain. This suggests that tumor-related symptoms may not be captured adequately by most study case report forms, making any assumptions about QOL benefits dubious. Thus, the true palliative benefit of chemotherapy in incurable cancers cannot be deduced from response rates, survival benefits and other traditional end points alone, but needs to be assessed directly, through validated patient-reported tools.

The QOL benefits seen in BR.21 are both statistically and clinically relevant, and correlated with response to erlotinib. The QOL benefits compare favorably with other studies using the same QOL questionnaire in first-line treatment of NSCLC, such as the study of cisplatinum-based versus noncisplatinum chemotherapy as first-line treatment for advanced NSCLC. Other studies that have reported QOL results for second-line chemotherapy describe small degrees of improvement, or more often less deterioration in the active therapy arm. Two studies reported on symptom and QOL effects of epidermal growth factor receptor inhibitors. In a nonrandomized study of 57 patients receiving erlotinib as second-line therapy, EORTC QOL questionnaires demonstrated improvements in pain and emotional functions, with responders to treatment showing sustained QOL for a longer time. In a phase II randomized study of 216 patients treated with gefitinib, Lung Cancer Symptom Scale (LCSS), and FACT-L (Functional Assessment of Cancer Therapy–Lung) questionnaires demonstrated 35% to 43% symptom improvement, particularly in pulmonary symptoms. The authors also describe correlation between symptom improvement and objective tumor response, with virtually all patients with partial remission showing symptom improvement, 61% to 81% of patients with stable disease reporting symptom improvement, and only 12% to 20% of patients with progressive disease reporting improvement.

In our study, the primary QOL outcome was prospectively defined as time to a clinically significant deterioration in three common lung cancer symptoms. There is no consensus as to which aspect of QOL should be the primary outcome of QOL analyses; we chose tumor-related symptoms because one of the most important goals of second-/third-line chemotherapy is to palliate symptoms. Patients with advanced NSCLC who have previously been treated with (and progressed during or relapsed after) chemotherapy are expected to deteriorate. In that clinical setting, a benefit may be defined not only as an improvement in baseline symptoms, but also as a delay in progression of symptoms. There is general agreement that the end points for QOL analyses should be predefined in all trials so that the QOL analysis is hypothesis testing, rather than hypothesis generating. All of the predefined primary analyses of this study...
demonstrated statistically significant and clinically relevant benefits in favor of patients receiving erlotinib. Secondary analyses of all QOL domains also demonstrated an advantage to patients on erlotinib, with significantly more patients showing improvement in global QOL and physical function, and trends towards improvements of other symptoms, such as fatigue. Of interest is the proportion of patients whose QOL and symptoms improved on the placebo arm. In the absence of active systemic therapy for these patients, improvement was likely a result of other supportive measures such as palliative radiotherapy, pain medications, and so on. However, despite improvements in some patients on the placebo arm, all of the disease and patient-centered outcomes consistently favored the erlotinib arm. Thus, this QOL analysis supports the true palliative benefit of erlotinib in improving not only survival, but also symptoms and QOL of patients with previously treated stage IV NSCLC.

Table 2. Quality-of-Life Response Analyses

<table>
<thead>
<tr>
<th>Domain/Item</th>
<th>Erlotinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>Improved</td>
<td>Stable</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role</td>
<td>357</td>
<td>31</td>
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<tr>
<td>Emotional</td>
<td>358</td>
<td>39</td>
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<tr>
<td>Cognitive</td>
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<tr>
<td>Social</td>
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<td>29</td>
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<tr>
<td>Global</td>
<td>352</td>
<td>39</td>
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<tr>
<td>Fatigue</td>
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<td>45</td>
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<tr>
<td>Nausea</td>
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<td>22</td>
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<tr>
<td>Pain</td>
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<td>42</td>
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<tr>
<td>Dyspnea</td>
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<td>34</td>
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<td>Sleep</td>
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<tr>
<td>Appetite</td>
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<td>25</td>
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<tr>
<td>Constipation</td>
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<td>Diarrhea</td>
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<tr>
<td>Financial</td>
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<td>31</td>
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<td>Cough</td>
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<td>44</td>
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<td>Hemoptysis</td>
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<td>Dyspnea Lung</td>
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<td>42</td>
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<tr>
<td>Cough</td>
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<td>7</td>
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<td>Swallowing</td>
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<td>12</td>
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<tr>
<td>Neuropathy</td>
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<td>27</td>
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<tr>
<td>Hair loss</td>
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<td>28</td>
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<tr>
<td>Chest pain</td>
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<td>30</td>
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<tr>
<td>Shoulder pain</td>
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<td>26</td>
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<tr>
<td>Pain elsewhere</td>
<td>274</td>
<td>32</td>
</tr>
<tr>
<td>Pain medication</td>
<td>174</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 3. Quality-of-Life Improvement According to Best Tumor Response

<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>CR + PR (n = 33)*</th>
<th>SD (n = 212)*</th>
<th>PD (n = 247)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Global</td>
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<td>63.6</td>
<td>90</td>
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<tr>
<td>Physical</td>
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<td>62.5</td>
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<td>Pain</td>
<td>22</td>
<td>66.7</td>
<td>98</td>
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<tr>
<td>Cough</td>
<td>18</td>
<td>72.0</td>
<td>90</td>
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<tr>
<td>Dyspnea</td>
<td>18</td>
<td>54.5</td>
<td>84</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *N refers to number of patients who had a response, and at least one change score for the global quality-of-life domain. The numbers for other domains or symptoms may vary by 1-4 patients, due to a few missing data, except for cough (item from lung cancer module, not available for all patients), where n = 25 for CR + PR, 187 for SD, and 204 for PD.
REFERENCES

Author Contributions

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