Symptom Assessment in Relapsed Small Cell Lung Cancer: Cross-Validation of the Patient Symptom Assessment in Lung Cancer Instrument

Lei Chen, MD, PhD, Lucia Antras, PhD,* Mei Sheng Duh, MPH, ScD,* Maureen Neary, PhD,† and Mary E. R. O'Brien, MD‡*

Introduction: Lung cancer symptoms can be burdensome for patients with small cell lung cancer (SCLC). Patient Symptom Assessment in Lung Cancer (PSALC), a self-report scale for assessing SCLC symptom burden, was developed and validated previously using intravenous topotecan clinical trial data. This study cross-validates the PSALC using oral topotecan (OT) trial data.

Methods: Data were analyzed from a randomized, open-label, multicenter trial including 71 patients with relapsed SCLC receiving OT with best supportive care and 70 patients receiving best supportive care alone. PSALC and EQ-5D were administered at baseline and at 3-week intervals. Internal consistency, reliability, construct validity, and responsiveness were evaluated.

Results: Only one factor was indicated in factor analysis, hence PSALC total score (PSALC-TS) was used for psychometric analysis. Internal consistency was supported by Cronbach's alpha of 0.78. Construct validity was supported by significant associations of higher PSALC-TS (higher symptom burden) with worse Eastern Cooperative Oncology Group performance status and by correlations of PSALC-TS with EQ-5D utility index and visual analog scale score (all $p < 0.001$). Reliability was supported by intraclass correlation coefficient of 0.68 (using PSALC-TS before clinical status change) and concordance correlation coefficient of 0.69 (using PSALC-TS at baseline and before first visit). PSALC-TS was responsive to clinical status change from baseline to tumor response (responsiveness statistic = −0.99) and to tumor progression (responsiveness statistic = 0.94).

Conclusions: Consistent with prior psychometric results, this cross-validation study using OT trial data showed acceptable validity, reliability, and responsiveness of the PSALC scale, further supporting its use to measure symptom burden in previously treated SCLC.

*Analysis Group, Inc., Boston, Massachusetts; †GlaxoSmithKline, Collegeville, Pennsylvania; and ‡Royal Marsden Hospital, Sutton, Surrey, United Kingdom.

Disclosure: L.C., L.A., and M.S.D. are employees of Analysis Group, Inc., which has received research funds from GSK. M.N. is an employee of GSK. M.E.R.O. has received honoraria and research support from GSK and has served as an advisor for GSK.

Address for correspondence: Mei Sheng Duh, MPH, ScD, Analysis Group, Inc., 111 Huntington Avenue, 10th floor, Boston, MA 02199. E-mail: mduh@analysisgroup.com

ISSN: 1556-0864/08/0310-1137

Key Words: Small cell lung cancer, Patient Symptom Assessment in Lung Cancer instrument, Clinical trials, Psychometric validation, Topotecan.

(*J Thorac Oncol.* 2008;3: 1137–1145)

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers.[1] Patients with SCLC usually experience a multitude of symptoms. Cough is the most common presenting and persistent symptom in about 75% of patients; the other common symptoms are dyspnea in about 60% of patients, chest pain in about 49% of patients, and hemoptysis in about 35% of patients. These symptoms often indicate the progression of the disease and are likely to affect patients' physical functioning and perception of the severity of their condition.[2,3]

SCLC is more aggressive than non-small cell lung cancer, metastasizes earlier and more quickly to regional and distant organ systems but is much more responsive to initial chemotherapy and radiation treatment.[1] Nevertheless, the majority of SCLC patients treated with standard first-line chemotherapy relapse after 1 year of treatment, and the prognosis for patients receiving second-line therapy is poor. Thereby, patients with SCLC may need to live with the reality of a shortened life span. The 2-year survival rate for patients with metastatic SCLC is approximately 15%.[4] For patients whose disease recurs after standard first-line platinum-based therapy, expected survival is measured in months, even with the most aggressive therapies.[5,6]

When the benefit of chemotherapy in extending life expectancy is limited, improving patients' health-related quality of life becomes an important goal of therapy. It has been shown that symptom burden and quality of life are well correlated; even in the absence of survival benefit, chemotherapy can provide palliative benefits to patients with lung cancer.[7] The association of lung cancer symptom burden and health-related quality of life warrants the assessment of lung-cancer-specific symptoms when evaluating the efficacy of a new treatment in clinical trials.

A number of instruments exist to measure lung-cancer-specific symptoms, including Lung Cancer Symptom Scale (LCSS),[8,9] Functional Assessment of Cancer Therapy—Lung (FACT-L),[10] and the European Organization for Research

and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) with Quality of Life Questionnaire Lung Cancer-13 (QLQ-LC13).[11,12] They differ in various aspects, such as symptom selection, the inclusion of global quality of life questions, type of assessment scales (i.e., visual analogue versus numerical rating scale). Although these instruments have been widely used since their introduction, they were originally validated in lung cancer populations that contain both patients with non-small cell lung cancer and also with SCLC, rather than exclusively in the population of SCLC patients. Because SCLC constitutes a minority of lung cancer cases, SCLC patients were likely underrepresented in the prior validation studies.

The Patient Symptom Assessment in Lung Cancer (PSALC) was initially developed for use in the registration trial of intravenous (IV) topotecan in treating patients with relapsed SCLC to specifically capture the symptom burden imposed on patients with SCLC, in particular among patients who failed first-line chemotherapy.[6] Using data from this prior trial, a recent publication demonstrated that the PSALC is a valid, reliable, and responsive symptom assessment questionnaire.[13]

Since its original development, the PSALC instrument has been used in over 900 patients in four multicenter clinical trials conducted in relapsed SCLC populations receiving not only the IV but also the oral formulation of topotecan. The objective of the current study is to cross-validate the PSALC instrument using the pivotal clinical trial data for oral topotecan (OT) to determine if the validity findings from the previous IV topotecan trial may also be replicated in this trial. Instrument validation is an ongoing process, such that establishing validity in additional population settings (e.g., in this study, in a subsequent clinical trial setting in relapsed SCLC) should further support the evidence base for the validity of the instrument.

MATERIALS AND METHODS

The Patient Symptom Assessment in Lung Cancer Instrument

The PSALC instrument contains nine items measuring the symptom burden experienced by patients with SCLC. It contains items related to lung-cancer-specific physical symptoms (i.e., "shortness of breath," "cough," "chest pain," "coughing up blood," "loss of appetite," "interference with sleep," "hoarseness," "fatigue") and an item related to the overall symptom burden of the disease with respect to functional status (i.e., "interference with daily activities"). According to the protocol of the clinical trial,[14] the PSALC was administered to the patients at baseline and before each subsequent clinical visit at 3-week intervals. Patients were asked to evaluate how much they had experienced each symptom (i.e., the extent to which they experienced it or were bothered by it) during the past 3 weeks on a four-point ordinal scale: 1 (not at all), 2 (a little), 3 (quite a bit), or 4 (very much). Thus, a higher score indicates greater symptom burden. Appendix shows the PSALC questionnaire.

Data Source

Data were used from an open-label, randomized, multicenter, phase III clinical trial in which OT in combination with best supportive care (BSC) ($N = 71$) was compared with BSC alone ($N = 70$) as second-line therapy for patients with relapsed SCLC. Details of the clinical trial results were published elsewhere.[14] At baseline, patients with an Eastern Cooperative Oncology Group (ECOG) score of 2 or lower, and adequate bone marrow, liver, and renal functions were recruited. It was recommended that patients receive at least four courses of OT, and the duration of the treatment depended on the tolerability and response. The primary end point of the study was overall survival (all-cause mortality). Secondary endpoints were tumor response rate, time to disease progression, symptom assessment (measured by the PSALC), quality of life evaluation (measured by the EQ-5D), and safety. Each patient's tumor response was evaluated by investigators independently as complete or partial response (CR/PR), stable disease (SD), or progressive disease (PD), according to the World Health Organization criteria. Nevertheless, because patients in the BSC alone arm were not receiving chemotherapy, it was not expected that these patients would show any response. Therefore, radiologic assessment of tumor response was only applied to patients randomized to receive OT plus BSC. The PSALC and EQ-5D were administered to patients in both treatment arms at the baseline and before each course of treatment, or approximately every 21 days.

Factor Analysis

To confirm that the PSALC contains only one factor as demonstrated in a prior validation study,[13] common factor analysis was first conducted. Using the Kaiser-Guttman rule, the number of factors was determined by the number of eigenvalues (a measure of how much of the variation in the data is accounted for by each factor) greater than one.[15–17] In addition, to estimate the contribution of each of the nine items to the factor or factors present in the instrument, final communality statistics were calculated. This step is needed to determine whether one aggregate score can be used in the validation analysis.

Internal Consistency

Three measures of internal consistency were calculated to assess the homogeneity of the scale. Pearson correlation coefficients were calculated for item-to-item correlation (between any two individual items) and item-to-total correlation (between a single item and the scale total excluding that item). In general, the threshold for a good item-to-total correlation is no lower than 0.20 to 0.40.[18,19] Cronbach's alpha coefficient reflects the average correlation among all the items in the scale. It was calculated for PSALC scores evaluated at the baseline and at four subsequent follow-up visits, separately. A "good" alpha is typically established by a value between 0.7 and 0.9.[20]

Test-Retest Reliability

The stability of a measure on the same patient from one time to another is a desirable feature of an instrument when