Identification of Patient-Relevant Non-Small Cell Lung Cancer (NSCLC) Symptoms Through Semi-Structured Qualitative Interviews

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INTRODUCTION:

- Lung cancer is among the most common cancers in terms of incidence. More than 220,000 new cases of lung cancer are projected to be diagnosed in the United States in 2015, with non-small cell lung cancer (NSCLC) representing approximately 85% of those cases. [1, 2]
- Lung cancer is also the leading cause of cancer-related mortality in the United States, projected to account for 158,040 deaths during 2015.[1]
- Because the severity of symptoms is directly related to the degree of impairment that patients experience, the assessment of NSCLC symptoms is an essential endpoint for clinical studies.
- By exploring the patient experience with NSCLC through qualitative interviews, it is possible to better understand and document the specific lung cancer-related concepts that are relevant to the patient as well as to understand the patient's assessment of improvement in his or her condition.
- Once documented through this concept elicitation process, identified concepts can be considered for inclusion in NSCLC-specific clinical outcome assessments (COAs).

OBJECTIVE:

- Complete qualitative concept elicitation interviews with patients diagnosed with NSCLC to support preliminary development of a patient-reported outcome (PRO) measure to assess treatment benefit in NSCLC clinical trials.

METHODS:

Study Population

- Recruitment was designed to enroll a diverse sample of patients similar to those who would be completing PRO instruments in future clinical trials of NSCLC treatments.
  - Recruitment quotas were employed to ensure appropriate representation of key subgroups within the NSCLC patient population, such as patients with early stage (I and II) tumors as well as those with comorbid chronic obstructive pulmonary disease (COPD). Beyond these specific recruitment quotas, each site targeted recruitment of a mix of patients with varying NSCLC-treatment histories, as well as broad representation across demographic characteristics such as age, sex, race/ethnicity, and educational attainment.
  - Subjects were recruited from 6 U.S. clinical sites in 6 states (AL, ID, IL, MT, ND, and NY).
- The eligibility criteria for the interview sample were designed to reflect common entry criteria for clinical trials in NSCLC:
  - **Inclusion Criteria:** Subjects were male or female and ≥18 years of age; had diagnoses of NSCLC; had an ECOG Performance Status of 0-2; were diagnosed with Stage I or II cancer and naïve to treatment for NSCLC --or- diagnosed with Stage III or IV cancer and either naïve to treatment for NSCLC or had recovered from any prior treatment-related toxicity/adverse events to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grade 1 (mild) or better; and were able to read, write, and speak English.
  - **Exclusion Criteria:** Subjects were excluded for severe clinically-significant mental health disorders or cognitive impairment; recent (12-month) history of clinically significant drug or alcohol abuse or dependence, excluding nicotine; current or recent (30 days) enrollment in any investigational device, drug, or biologics product study; or having any medical condition or disorder that could compromise his/her ability to give written informed consent and/or prevent or interfere with the patient's ability to successfully participate in a face-to-face interview and provide meaningful and non-confounded information about their lung cancer experience.

Concept Elicitation (CE) Interviews

- Semi-structured qualitative interviews[3] were conducted by trained research staff with a non-random purposive sample of adult patients in the US diagnosed with Stage I-IV NSCLC.
  - Interviews followed a pre-approved interview guide and used open-ended questions and day-reconstruction exercises to elicit spontaneous reports of symptom/impact concepts.
  - Subsequent probing was used to assess concepts not spontaneously reported by subjects.
  - Subjects were asked to rate the severity and level of bother or difficulty for reported symptoms and impacts using 0-10 numerical rating scale exercises.
  - To guide item development, subjects were also asked about appropriateness of measuring the severity, frequency, or duration of each concept.

Content Analysis

- All interview sessions were audio recorded and transcribed.
- The concept elicitation interview transcripts were coded and analyzed by trained qualitative coders using Atlas.ti, and were summarized by like-content using an iterative coding framework.
  - Coded concepts were grouped by similarity of content and analyzed to identify the most relevant expressions and most common language used by patients.
- A Saturation Grid was used to track symptoms and impacts expressed during the interviews and assess saturation of concept.
  - Transcripts were ordered chronologically in groups of 8 transcripts. Codes from each group were compared with previous groups to determine whether any new additional unique concepts emerged.

RESULTS:

Study Sample

- A total of 51 subjects participated in the CE interviews.
- The subjects were an average of 64.9 years old, were 51% female, and 75% non-Hispanic white (Table 1).
- Fifty-one percent of subjects had Stage IV disease and 37% had Stage III disease at the time of the interview. Thirty-five percent of subjects had a documented diagnosis of COPD, and 39% were naïve to treatment for NSCLC (Table 1).
- Review by a clinical expert panel determined the sample demographic and clinical characteristics to be aligned with those of populations expected to participate in clinical trials investigating new treatments for NSCLC.

Qualitative Content Analysis Results

- Analysis of the transcripts resulted in 1,897 coded expressions of NSCLC-related symptoms.
- Expressions were coded and grouped into 43 symptom concept groups within 5 hypothesized symptom sub-domains.
- Inter-rater agreement was assessed in five dual-coded transcript pairs, and observed to be high with 89.1 to 91.2% agreement between raters for the identification of symptom concepts being expressed in the transcripts, and 95.9 to 98.9% agreement between raters on code assignment for identified concepts.
- Saturation of concept (the point at which no new symptom concepts were elicited) was achieved after the 27th of the 51 coded transcripts (i.e., the third of six transcript groups).

Table 1: *Demographic and Clinical Characteristics of Participants*

Characteristic	Total Subjects N=51 (100%)
Age in years: mean(SD); [range]	65 (11); [48-88]
Gender: Female: n (%)	26 (51%)
Ethnic Group: n (%)	
Hispanic, Latino or Spanish Origin	5 (10%)
Non-Hispanic or Latino	46 (90%)
Race: n (%)	
Asian	2 (4%)
Black or African American	8 (16%)
White	38 (75%)
Other Race or Multiple Races†	3 (6%)
Highest Level of Education Completed: n (%)	
Less than High School	3 (6%)
High School	25 (49%)
Some College	13 (26%)
Bachelor's Degree	3 (6%)
Graduate or Professional School	7 (14%)
NSCLC Stage (at time of screening/interview)	
I	6 (12%)
II	---
III	19 (37%)
IV	26 (51%)
ECOG Performance Status	
0	17 (33%)
1	24 (47%)
2	10 (20%)
Current Line of NSCLC Treatment	
Early stage (treatment-naïve)	19 (37%)
1st line advanced/metastatic	18 (35%)
2nd line advanced/metastatic	9 (18%)
3rd line advanced/metastatic	3 (6%)
Other: Observation, Subsequent	2 (4%)
Comorbid COPD	
Diagnosis Present	18 (35%)
Smoking Status / History	
Current smoker	7 (14%)
Ex-smoker	36 (71%)
Never a regular smoker	8 (16%)
Mean (SD) Number of Pack Years Smoked	33 (22)

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Table 2: *Summary of Coded NSCLC Symptom Expressions*

NSCLC Symptom Sub-Domains and Concepts	Number of Patient Expressions of Concept	% of Total Symptom Expressions (N=1,897)	Number of Transcripts Contributing to Concept Expression	% of Transcripts Contributing (N=51)
Fatigue and Tiredness	**317**	**17%**		
Exhaustion	16	0.8%	7	13.7%
Fatigue	56	3.0%	20	39.2%
Low Energy	41	2.2%	15	29.4%
Low Stamina	10	0.5%	7	13.7%
Tiredness	172	9.1%	39	76.5%
Weakness	22	1.2%	11	21.6%
Pain and Discomfort	**226**	**12%**		
Back Pain	47	2.5%	12	23.5%
Bone Pain	9	0.5%	6	11.8%
Chest Pain	67	3.5%	17	33.3%
General Pain	59	3.1%	18	35.3%
Muscle Pain	39	2.1%	13	25.5%
Other Pain Symptom Concepts*	5	0.3%	3	5.9%
Respiratory / Pulmonary Symptoms	**676**	**36%**		
Bronchitis	18	0.9%	9	17.6%
Coughing Up Blood	56	3.0%	12	23.5%
Coughing	206	10.9%	41	80.4%
Difficulty Breathing	91	4.8%	21	41.2%
Emphysema	9	0.5%	7	13.7%
Phlegm	46	2.4%	16	31.4%
Pneumonia	62	3.3%	16	31.4%
Shortness of Breath	149	7.9%	35	68.6%
Wheezing	35	1.8%	12	23.5%
Other Respiratory Symptom Concepts**	4	0.2%	3	5.9%
Digestive Symptoms	**200**	**11%**		
Appetite	92	4.8%	26	51.0%
Diarrhea	12	0.6%	5	9.8%
Difficulty Swallowing	16	0.8%	7	13.7%
Nausea	51	2.7%	15	29.4%
Vomiting	19	1.0%	6	11.8%
Other Digestive Symptom Concepts†	10	0.5%	3	5.9%
Other Symptoms	**473**	**25%**		
Cognition	41	2.2%	12	23.5%
Dizziness and Fainting	35	1.8%	11	21.6%
Headache	17	0.9%	6	11.8%
Heart Problems	12	0.6%	3	5.9%
Heat Sensitivity	33	1.7%	8	15.7%
Hoarseness	49	2.6%	20	39.2%
Immunity Lessened	37	2.0%	12	23.5%
Lump	19	1.0%	5	9.8%
Numbness	25	1.3%	8	15.7%
Restlessness	5	0.3%	2	3.9%
Feeling Sick	6	0.3%	7	13.7%
Skin Change	14	0.7%	3	5.9%
Sore Throat	7	0.4%	3	5.9%
Swelling	31	1.6%	12	23.5%
Taste Change	15	0.8%	5	9.8%
Twitching	14	0.7%	3	5.9%
Voice Change	32	1.7%	8	15.7%
Weight Loss	53	2.8%	22	43.1%
Other Symptom Concepts ‡	28	1.5%	18	35.3%

*Other pain symptom concepts edited from patients include: gassy pain, hernia, and tooth pain.
**Other respiratory symptom concepts edited from patients include: congestion, pulmonary fibrosis, and weak lungs.
†Other digestive symptoms edited from patients include: acid reflux, constipation, stomach issues.
‡Other symptoms edited from patients include: bloody nose, brain metastases, burns, dehydration, dry mouth, hot flas, itching, tongue soreness, vision problems, being cold, fidgeting, hearing difficulties, weight gain, mouth sores, and deep vein thrombosis.

Concept Elicitation Findings

- The most frequently reported symptom concept was **Coughing** (N=206 total expressions, including those made spontaneously as well as in response to probes). This represents 10.9% of the total number of coded symptom expressions (N=1,897), and expressions about **Cough** were contributed by 41 (80%) of the 51 subjects (see Table 2).
- After coughing, the next most predominant symptom concepts expressed in interviews were **Tiredness** (172 expressions from 39 different subjects) and **Shortness of Breath** (149 expressions; 35 subjects). These concepts were followed by **Poor Appetite, Weight Loss, Difficulty Breathing, Fatigue, Hoarseness, General (Non-Chest) Pain,** and **Chest Pain** (Table 2).
- The symptom concept most often mentioned spontaneously was **Coughing** (by N=29 subjects). Other symptom concepts most frequently reported spontaneously (rather than upon probing by the interviewer) were **Shortness of Breath** (N=22), **Chest Pain** (N=14), **General Pain** (N=8), **Tiredness** (N=12), **Difficulty Breathing** (9), and **Poor Appetite** (11).
- **Numbness** (mean of 8.7 [SD=1.2] out of 10). **Taste change** (8.5 [2.1]), **Dizziness** (8.4 [1.1]), and **Exhaustion** (8.0 [2.0]) were rated by patients as the most bothersome symptoms. Among the most frequently-expressed symptoms above, **Poor Appetite** (6.9 [1.9]), **Shortness of Breath** (6.9 [2.5]), and **Tiredness** (6.8 [2.2]) received the highest ratings of bother.
- Across all concepts, the highest average severity ratings were observed for **Lost Ability to Taste** (mean rating of 10 out of 10, but only offered and rated by one person) and **Dizziness** (mean rating of 8.8 [SD=1.0]).

  Among the frequently-expressed concepts highlighted above, **General Pain** (8.0 [2.3]), **Poor Appetite** (7.5 [2.4]), and **Chest Pain** (7.1 [2.7]) were rated as the most severe.

CONCLUSIONS:

- Relevant patient-reported NSCLC symptom concepts were identified through qualitative interviews with 51 patients.
- Evidence for the patient-relevance of identified symptom concepts was demonstrated through both spontaneous and probed expression as well as patient-based ratings of severity and level of bother. This evidence of content validity is further supported by achievement of concept saturation.
- Interview findings provide evidence to suggest **Cough, Difficulty Breathing, Shortness of Breath, Pain** (both chest-specific and general), **Fatigue, Tiredness/Tiring Easily,** and **Poor Appetite** as key patient-expressed symptom concepts that should be considered as potential candidates for PRO assessment in NSCLC.

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