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Patient-reported Outcomes from Patients Receiving Immunotherapy or Chemo-immunotherapy for Metastatic Non-Small Cell Lung Cancer in Clinical Practice

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Abstract

Introduction: Immunotherapy and chemo-immunotherapy clinical trials for metastatic non-small cell lung cancer (mNSCLC) have generally excluded patients with poor performance status (PS) and utilized patient reported measures that could miss some symptoms associated with

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immunotherapy. The goals of this study were to describe quality of life and symptom burden among mNSCLC patients on immunotherapy in clinical practice and to examine burden by PS and age.

Methods: Between 2017 and 2018, mNSCLC patients on immuno/chemo-immunotherapy at an academic medical center completed the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and the National Cancer Institute Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events™ (PRO-CTCAE™). Univariate and bivariate analyses described EORTC-QLQ-C30 subscales and the proportion reporting at least moderate PRO-CTCAE™ symptoms and compared scores by PS (ECOG 0/1 vs. 2/3) and age (<70 vs. ≥70 years).

Results: Sixty patients (60% female; 75% <70 yo; 68% PS 0/1; 57% receiving single agent immunotherapy) participated. The mean EORTC-QLQ-C30 global health score was 62.6; EORTC symptoms were highest for fatigue, insomnia, dyspnea, and financial concerns (all >30). Global health and pain were worse in PS 2/3 patients. On the PRO-CTCAE, 20–40% reported at least moderate gastrointestinal, respiratory, dermatologic, arthralgia, or myalgia symptoms. The PRO-CTCAE™ pain score was higher among PS 2/3 patients.

Conclusions: In clinical practice, global health was largely comparable to published clinical trials, but PRO-CTCAE™ items indicated a higher symptom prevalence. Closer monitoring of symptoms is warranted in PS 2/3 patients.

MicroAbstract

The quality of life and symptom experience for metastatic lung cancer patients treated with immunotherapy or chemo-immunotherapy in routine care has not been described. In our survey of 60 metastatic lung cancer patients on these treatments, 20–40% reported moderate symptoms (e.g., rash, muscle ache). Patient-reported outcomes need to be monitored in clinical practice, especially for patients with worse physical function.

Keywords

patient-reported outcomes; immunotherapy; pembrolizumab; nivolumab; atezolizumab; health-related quality of life; lung cancer

Background

With recent FDA approvals, single agent immunotherapy or chemo-immunotherapy is given in the first or second line setting for the majority of patients with metastatic non-small cell lung cancer (mNSCLC) with performance status (PS) of 0–2. Adverse event (AE) data from clinical trials suggest single agent immunotherapy confers a favorable toxicity profile compared to chemotherapy and support the tolerability of chemo-immunotherapy.[1–7] In some trials, AE data have been complemented by patient-reported outcome (PRO) data, which capture a patient's status directly from the patient to provide information about symptoms and health-related quality of life.[8,9] PRO data are important complements to AE data, as physician graded AEs can underestimate symptom burden.[10,11] Encouragingly, PRO data from trials suggest immunotherapy is associated with better overall health-related

quality of life and greater time to deterioration with respect to some symptoms (e.g., chest pain) and functional domains (e.g., role function) when given as a single agent[12–15] or in combination with chemotherapy[16] as compared to chemotherapy alone. However, most of these trials have not administered PRO measures of potential immune-mediated symptoms such as pruritus, arthralgia, and myalgia, limiting our understanding of patients' experience of these symptoms.[17,18] Further, the majority of clinical trials involving immunotherapy in metastatic NSCLC have excluded patients with a PS of 2 or higher. Yet in clinical practice, an estimated 30% of lung cancer patients have a PS 2 or higher, and many are older with multiple comorbidities, which may affect treatment tolerability.[19–21] Therefore, questions remain about the quality of life and symptom burden experienced by patients with mNSCLC who receive immunotherapy or chemo-immunotherapy outside of the clinical trial setting.

The goals of this study were two-fold: 1) to characterize self-reported quality of life and symptoms, including symptoms that could be associated with immunotherapy in routine clinical practice, and 2) to examine quality of life and symptom severity based on performance status (0/1 vs. 2/3) and age (< 70 years vs. ≥70 years). We chose these strata to investigate how patients who are often excluded (e.g., PS 2/3) or underrepresented (e.g., age ≥70 years) in clinical trials may be experiencing treatment. We hypothesized that patients with worse performance status (PS 2/3) and of older age (≥70 years) would report worse quality of life and greater symptom burden. An exploratory aim was to determine whether quality of life and symptoms differed based on whether a patient was currently receiving mono-immunotherapy vs. chemo-immunotherapy. We hypothesized that patients on chemo-immunotherapy would report worse quality of life and greater symptom burden due to the potential for added toxicities. These cross-sectional results will inform priority areas for patient-reported assessment in clinical trials, symptom monitoring domains, and supportive care in clinical practice.

Methods

Study Design

Between October 2017 and July 2018 we recruited metastatic NSCLC patients undergoing immunotherapy in an academic medical center to complete a cross-sectional survey. To obtain a sample of patients earlier and later in treatment, patients were purposively sampled[22] (i.e., recruited by strata) based on whether they had been re-imaged for treatment response. The re-imaging variable was of analytic interest for a separate study objective related to patient treatment expectations. Patient survey data were supplemented with clinical data abstracted from the electronic medical record. Patients were compensated with a $30 gift card for completing the survey.

Participants

Eligibility criteria included: (a) histologically or cytologically documented NSCLC stage IV (de novo or recurrent metastatic per AJCC 7th edition staging); (b) Eastern Cooperative Oncology Group performance status 0–3/Karnofsky performance status 60–100; (c) receipt of immunotherapy with or without chemotherapy; (d) ability to provide informed consent in English. Potentially eligible patients were called prior to clinic appointments or approached

in clinic. Interested patients provided verbal consent, including a consent to a HIPAA release for clinical information from the electronic medical record. This study was approved by the Wake Forest University Health Sciences Institutional Review Board (#46256) and Wake Forest Baptist Comprehensive Cancer Center (#01517).

Measures

Sociodemographic Variables

Patients self-reported their sex, education, relationship status, race, ethnicity, income, employment status, and health insurance status. Rural residence was determined according to the Federal Office of Rural Health Policy's eligible ZIP codes, where any ZIP code with more than 50% of the population residing in a non-metro county or rural census tract was deemed rural.[23] Patient smoking history and status was assessed with the 4-item base of the Cancer Patient Tobacco Use Questionnaire (C-TUQ).[24] Patients were considered currently smoking if they reported smoking within the past week on the C-TUQ.

Clinical Data

Data obtained from the electronic health record included: patient age, date of diagnosis, performance status ("good" PS defined as ECOG 0–1, "poor" PS as ECOG 2–3; extracted from most recent treatment note, typically 1–4 weeks prior to completing the survey), date of first immunotherapy treatment, cancer treatment history (e.g., prior treatment, line of treatment), response to treatment (defined as patients who had either radiographic partial or complete response by study investigators using RECIST criteria[25]) and disease variables (e.g., de novo vs. recurrent metastatic). Multimorbidity was summarized using the Charlson Comorbidity Index (without points for cancer diagnoses, with higher scores indicating a greater burden of noncancer comorbidities),[26] based on ICD-10 diagnosis codes.[27] Charlson scores were dichotomized (at least 1 non-cancer comorbidity vs. 0 non-cancer comorbidities).

EORTC Health-Related Quality of Life and Symptoms

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC-QLQ-C30[28]) was used to measure both health-related quality of life and symptoms. The global health and five functional domains (physical, role, emotional, cognitive, and social) from the EORTC-QLQ-C30[28] were used to measure health-related quality of life. Symptom subscales from the EORTC-QLQ-C30[28] included fatigue, insomnia, dyspnea, financial concerns, pain, appetite, constipation, nausea, and diarrhea). Items were rated on a four-point scale with 1 = *not at all* to 4 = *very much*. Subscales were transformed linearly to have a range of 0–100, with higher scores reflecting better function on the 5 functional scales or a higher symptom burden on the symptom scales. Internal consistency in this sample was acceptable (Cronbach's α = .66 to .89).

NCI-PRO-CTCAE™ Symptoms

The nine symptom subscales of the EORTC-QLQ-C30 were supplemented with items from the National Cancer Institute Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events™ (NCI-PRO-CTCAE™) [29,30] to help assess

potential immune-mediated side effects patients may experience on immunotherapy or chemo-immunotherapy. Selected PRO-CTCAE™ items assessed the past week's severity or frequency of symptoms, with follow-up questions (e.g., symptom interference) as indicated. Analyses focused on the severity or frequency base item for each symptom. Severity items included: constipation, fatigue, cough, wheezing, dyspnea, dry skin, itchy skin, and decreased appetite (0 = none to 4 = very severe). Frequency items included: diarrhea, bowel incontinence, abdominal pain, pain, myalgia (muscle ache/pain), arthralgia (joint ache/pain), arm or leg swelling, and nausea (0 = never to 4 = almost constantly in the past week). Rash was assessed as "yes"/"no." An item score of "2" or higher ("moderate"/"occasionally" to "very severe"/"almost constantly") was used to indicate at least moderate/occasional symptoms. Items were selected with input from multiple thoracic oncology physicians at the Wake Forest Baptist Comprehensive Cancer Center and review of the available literature on symptom trajectories in immunotherapy.

Statistical Analyses

We computed univariate means, medians, and standard deviations (for continuous/interval variables) and percentages (for categorical variables) to describe the sociodemographic, clinical, quality of life, and symptom characteristics of our sample. We also conducted bivariate tests comparing patients within strata of age and performance status on these variables. Chi-square tests (or Fisher's exact test when indicated by cell size) were used for categorical variables while 2-sample t-tests were used for continuous/interval variables. A two-tailed alpha of 0.05 was used throughout. All analyses were conducted in SAS 9.4.

Results

Study Population

Sixty-seven eligible patients were contacted, of whom 60 consented to participate. Reasons for refusal included: "too much going on right now" or "do not feel well enough" (n = 2), "no reason – hung up the phone prior to describing study" (n = 1), "lost to coordinator follow-up" (n = 1), or "not specified" (n = 3).

Sociodemographic and clinical characteristics appear in Table 1. The mean patient age was 62.5 years (SD = 9.3 years); 25% (n = 15) were 70 years of age or above. The sample was predominantly female, white, and married. More than half had completed at least some college, though many had a high school diploma or less as their highest educational level. The majority of the sample had an annual household income of less than $50k. Nearly all had smoked in their lifetime; 25% had smoked in the past week. The average pack year history was 32.7 (SD = 21.1). Most had an ECOG PS of 0/1, presented with de novo stage IV NSCLC, were on pembrolizumab (with or without chemotherapy), and had undergone prior therapy; 57% (n = 34) were on single agent immunotherapy (pembrolizumab alone, nivolumab, or atezolizumab). Half had at least one non-cancer comorbidity. Patients had been on immunotherapy (with or without chemotherapy) an average of 29 weeks (SD = 31 weeks; median 20.8 weeks; range = 0 – 143 weeks). Roughly 60% had received a scan to assess treatment response; of these, approximately 30% were responding to treatment.

Baseline age and PS were not related (27% of patients age 70+ had a PS 2/3 vs. 33% of patients ≤70, p=0.75). Age and performance status were not significantly different among those who were on immunotherapy vs. chemo-immunotherapy (see Supplemental Table 1). Results that follow are presented for the overall sample by age and performance status strata, with supplemental tables describing results by treatment strata (i.e., immunotherapy vs. chemo-immunotherapy).

Global Health-Related Quality of Life, Function, and Symptoms (EORTC-QLQ-C30; Table 2)

Global health-related quality of life, function, and symptom scores from the EORTC-QLQ-C30 for the overall sample and by performance and age strata appear in Table 2. The global health score on the EORTC-QLQ-C30 was 62.6 (SD = 21.5; possible scores = 0–100 with higher scores reflecting better quality of life). Of the 5 functional domains on the EORTC-QLQ-C30, cognitive function was the highest score (M=81.7, SD=21.0), while role function was the lowest score (M=70.0, SD=32.3). As shown in Table 2, patients with worse performance status reported significantly worse global health (M = 51.8 PS 2/3 vs. M = 67.7 PS 0/1, p = .006), physical function (M = 62.1 PS 2/3 vs. M = 80.2 PS 0/1, p = .001), and role function (M = 57.9 PS 2/3 vs. M = 75.6 PS 0/1, p = .047). Patients who were 70 years of age or older reported similar global health (M = 65.6 age 70+ vs. M = 61.7 age <70, p = .55), but better social function (M = 85.6 age 70+ vs. M = 69.6 age <70, p = .008) compared to those who were less than 70 years of age.

Of the EORTC-QLQ-C30 symptom scales (Table 2: range = 0–100 with higher scores indicating greater symptom severity), scores were highest for fatigue (M= 39.6, SD=28.5), insomnia (M=37.9, SD= 36.6), dyspnea (M= 35.0, SD=29.7), and financial concerns (M= 32.8, SD= 36.0). Patients with worse performance status reported significantly more pain (M = 45.6 PS 2/3 vs. M = 19.9 PS 0/1, p = .006). There were non-significant differences by PS level for fatigue (M = 49.1 PS 2/3 vs. M = 35.2 PS 0/1, p = .08), dyspnea (M = 43.9 PS 2/3 vs. M = 30.9 PS 0/1, p = .12), and diarrhea (M = 15.8 PS 2/3 vs. 4.9 PS 0/1, p = .12). There were no statistically significant differences in dyspnea, fatigue, or pain scores on the EORTC-QLQ-C30 by age group. However, those 70 years of age or older reported less nausea (M = 3.3 age 70+ vs. 14.1 age <70, p = .007) and diarrhea (M = 2.2 age 70+ vs. 10.4 age <70, p = .046). There was a relatively large, though nonsignificant, difference on financial concern (M = 20.0 age 70+ vs. 37.0 age <70, p = .11).

Health-related quality of life, function, and symptom scales on the EORTC-QLQ-C30 did not differ statistically between those who were on immunotherapy alone and those who were on chemo-immunotherapy (Supplemental Table 2), with the exception of decreased appetite (immunotherapy M = 33.3, SD = 36.5; chemo-immunotherapy M= 11.9, SD = 20.7, p = .007). EORTC-QLQ-C30 scales were not related to weeks on immunotherapy/chemo-immunotherapy (data not shown).

Past Week Symptoms Reported on the NCI-PRO-CTCAE™

Past week symptoms on the PRO-CTCAE™ were examined for the entire sample, including those who were on chemo-immunotherapy. Patient reports of at least moderate/occasional symptoms experienced in the past week according to the PRO-CTCAE™ for the overall

sample and by performance (PS 0/1 vs. 2/3) and age (<70 yo vs. ≥ 70 yo) strata appear in Table 3. Table 3 results are for the base question of each symptom. Follow-up questions about a symptom were only answered if a patient reported a symptom was present. See Supplemental Table 3 for the means, standard deviations, and observed range of PRO-CTCAE™ items.

As shown in Table 3, the most prevalent symptom (where symptom was defined as at least moderate/occasional, i.e., values of "2" or higher on the ordinal rating scale) experienced in the past week on the PRO-CTCAE were fatigue (50%), pain (41.7%), muscle ache (40%) and joint pain (33%); other common symptoms included rash, cough, dyspnea, dry skin, itchy skin, constipation, and diarrhea. A higher proportion of PS 2/3 patients (68.4%) reported at least occasional pain compared to those with a performance status of 0/1 (29.3%, p =.004; Table 3). There were relatively large though non-significant differences by PS group in percent reporting at least moderate cough (42.1% for PS 2/3 vs 17.1% among PS 0/1, p =.06), occasional diarrhea (31.6% vs. 12.2%, p = .09), occasional joint pain (47.4% vs. 26.8%, p = .12), and decreased appetite (36.8% vs. 17.1%, p = .11). There were no statistically significant differences in reporting at least moderate/occasional PRO-CTCAE™ symptoms between those age 70 years or above compared to those less than 70 years of age.

When we stratified on treatment factors (Supplemental Table 4), we found that a significantly higher proportion of patients who were currently on immunotherapy alone reported at least occasional abdominal pain (22.6% vs. 0%, p = .01) and at least moderately decreased appetite (35.5% vs. 10.7%, p = .03) compared to those who were on chemo-immunotherapy. A higher proportion of those who were on chemo-immunotherapy reported at least occasional arm or leg swelling (21.4% of those on chemo-immunotherapy vs. 3.2% of those on immunotherapy, p = .045). More of those who were on immunotherapy alone reported at least moderate shortness of breath but this difference was not statistically significant (32.3% of those on immunotherapy alone vs. 14.3% of those on chemo-immunotherapy, p = .11). Time on immunotherapy/chemo-immunotherapy was not related to reporting of moderate or greater PRO-CTCAE™ symptoms.

We also examined the proportion of patients who reported high levels of symptoms in the past week (i.e., item score "3" or "4"; Supplemental Table 5). The most prevalent were pain (26.7%), joint pain (15%), muscle ache (13.3%), and fatigue (13.3%).

Discussion

To date, the only available PROs for metastatic NSCLC patients receiving immunotherapy fail to assess some concerns such as dermatologic symptoms that could be associated with immunotherapy. These studies also have been limited to samples that may not adequately represent patients in the broader patient population presenting for treatment (i.e., patients with worse PS and older age). The goals of this study were to describe patient-reported quality of life and symptom burden among patients on immunotherapy with or without chemotherapy in clinical practice and to examine burden among patients with PS 2/3 and 70 years of age or older. These patients represent a meaningful proportion of lung cancer patients.[19–21] The worst average function scores occurred in the social and role domains.

Global health-related quality of life, physical function, role function, and pain were worse among PS 2/3 patients, but did not differ by age. At least a third of patients reported moderate or occasional past week experiences of fatigue, myalgia, and arthralgia on the PRO-CTCAE™, and these symptoms did not appear to differ by PS or age. Overall, our results suggest the need for close symptom monitoring among PS 2/3 patients and for future trials to measure symptoms not captured on the EORTC-QLQ-C30 that could be associated with immuno- and chemo-immunotherapy.

Most immuno- and chemo-immunotherapy trials in metastatic NSCLC have utilized the EORTC-QLQ-C30 to measure health-related quality of life and symptoms.[12–16,18] Longitudinal designs and similar assessment time frames are needed to compare quality of life and symptom experiences of patients treated in clinical practice to those treated on clinical trials. However, to help contextualize our findings, we offer a limited comparison of EORTC-QLQ-C30 results observed in our study to those available from clinical trials. Our sample's global health score on the EORTC-QLQ-C30 (i.e., 63) was similar to global health scores from trials of second-line single agent immunotherapy follow-up (e.g., 65–67[12]), but somewhat worse compared to first line single immunotherapy follow-up (71 pembrolizumab alone[13]). Insomnia and financial scores were meaningfully worse (i.e., > 10 points worse)[31] in the current sample (38 for insomnia in current sample v. 26 in OAK; 32 for financial vs. 18 in OAK).[14] The higher scores for financial concerns in this sample compared to trials' may be attributable to multiple factors, including the high prevalence of relatively low socioeconomic status in this sample and potential differences in out-of-pocket treatment costs for patients in routine clinical practice compared to clinical trials. Regardless, the potential financial hardship associated with expensive treatment regimens such as immunotherapy should be assessed going forward, especially in patients with low socioeconomic status who are often underrepresented in trials.[32]

The likely differences between clinical trial participants and lung cancer patients in routine clinical practice motivated our examination of health-related quality of life by PS and age. Not surprisingly, PS 2/3 patients reported worse global quality of life and worse dyspnea, fatigue, and pain on the EORTC-QLQ-C30, all of which were worse compared to clinical trial samples (dyspnea = 44 vs. 32 in OAK [second line single agent atezolizumab][14]; fatigue = 49 vs. 36 in OAK[14]; and pain = 46 vs. 29 in OAK[14]). In contrast to PS comparisons, patients age 70 years or older reported similar or better quality of life and symptom burden on the EORTC-QLQ-C30 compared to those younger than 70.[12–14] In exploratory analyses of EORTC-QLQ-C30 subscales based on treatment strata (immunotherapy vs. chemo-immunotherapy) we did not find many significant differences. Although the immunotherapy and chemo-immunotherapy patients appeared comparable on a number of sociodemographic and clinical variables, our dichotomization of patients in these two groups was based on a one-time cross-sectional review of current therapy, and thus did not account for potential heterogeneity within groups related to issues like prior dose reductions or discontinuation of chemotherapy for specific reasons related to symptoms.

At the time we conducted this study, patient-reported quality of life measures that were specific to immuno- and chemo-immunotherapy had not been developed. We administered PRO-CTCAE™ items to capture symptoms that could be associated with immunotherapy

(e.g., rash, myalgia). We did not have patient input on which items to include, nor did we have data on physician-rated adverse events, which are important complements to and often diverge from PRO-CTCAE™ data.[10,11] Still it is worth noting that nearly all symptoms on the PRO-CTCAE™ were more prevalent at moderate to high levels (i.e., scores 2–4) than *any grade* CTCAE from therapeutic trials[1–6] (e.g., 40% reported at least moderate myalgia in the current sample vs. 2–14% any grade myalgia[2–4,6]). To our knowledge, this is the first study to describe many of these symptoms in this setting. The relatively high prevalence of symptoms suggests need for further inquiry. Specifically, the fact that at least 20% of patients reported moderate to high levels of constipation, fatigue, pain, cough, dyspnea, rash, dry skin, itchy skin, arthralgia, myalgia, and decreased appetite on the PRO-CTCAE, and 10% reported high levels of pain, arthralgia, myalgia, and fatigue raises questions about comorbidities, other clinical factors, and whether symptoms are under-assessed in clinical practice. In exploratory analysis, different constellations of symptoms were associated with different patient subgroups. PS 2/3 patients were more likely to have pain, cough, arthralgia, diarrhea, and decreased appetite. Patients receiving immunotherapy alone were more likely to have abdominal pain and decreased appetite. Interestingly, the older age subgroup (≥70 yo) did not have noticeable differences in the frequencies of particular symptoms compared to the younger group. These analyses should be considered hypothesis-generating given the small sample sizes within strata and the likely existence of confounding with other clinical variables.

Our results suggest the need for future research on health-related quality of life and symptom burden among patients with worse performance status who are receiving immunotherapy and chemo-immunotherapy. Results also align with concerns that patient-reported outcome data on immuno/chemo-immunotherapy for metastatic NSCLC have not assessed some symptoms that might be more prevalent with this treatment regimen.[17] Our data cannot inform whether symptoms we observed were due to treatment, disease, or comorbidity. There is a broad range in type and severity of potential toxicities associated with immunotherapy, many of which can be difficult to differentiate from disease or comorbidity. For example, in contrast to endocrine toxicities, which can be clearly identified through laboratory values, the symptoms of pulmonary toxicity (cough, dyspnea, hypoxia) can be easily misattributed to disease burden or lung comorbidity. Similarly, the specific characteristics of myalgia and arthralgia can be difficult to differentiate from non-inflammatory pain syndromes (e.g fibromyalgia) and arthritic pain.[33] The attribution of these symptoms is an important inquiry for future trials and longitudinal data from clinical practice. Still, regardless of attribution, the high prevalence of symptoms in this sample suggests the need for assessment and close monitoring in clinical practice to trigger appropriate clinical workup and multidisciplinary management.[34,35] Patient-reported monitoring and other tools such as geriatric assessment may bolster clinical management. PRO monitoring may be especially important for symptoms that may be due to prevalent under-managed comorbidities like COPD[36,37] or symptoms such as rash or vitiligo, which tend to be underestimated, but may be quite bothersome to patients.[38] Verbal feedback from patients in this study suggested vitiligo may be of particular concern among African American patients.

Limitations

Given the cross-sectional design of the study, we are unable to discern whether patient symptoms were present before immunotherapy treatment or resulted from treatment. A longitudinal design capturing pre and post-treatment symptom burden and quality of life is necessary to address this critical question. This study also was limited by a small sample size recruited from one academic medical center and is subject to some self-selection bias. The lack of observed differences based on performance status and age group could be due to a lack of statistical power, particularly for moderate to high symptoms on the PRO-CTCAE™. The amount of time between obtaining a patient's PS from the medical record and collecting PROs varied. Further, the sample was heterogeneous with respect to treatment factors (e.g., immunotherapy agent, chemo-immunotherapy vs. single agent immunotherapy, prior treatments, time on treatment). Future studies should examine these treatment factors and other relevant variables such as smoking status. Finally, at the time we conducted this study, there was not a validated patient-reported measure of health-related quality of life specific to immunotherapy or chemo-immunotherapy. We selected items from the PRO-CTCAE™ that we thought could capture potential symptoms associated with immunotherapy. Due to concerns about respondent burden, we did not administer the lung cancer module that complements the EORTC-QLQ-C30, which could have provided information about chemotherapy symptoms. Future studies of PROs in immunotherapy and chemo-immunotherapy should consider including the LC13 modules of the EORTC-QLQ-C30, administer the PRO-CTCAE™ with the CTCAE to provide complementary understanding of symptoms experienced, and administer new health-related quality of life measures that are developed with patient and physician input to capture the effects of this treatment regimen.

Conclusion

This study is among the first to report patient-reported outcomes among lung cancer patients receiving immunotherapy and chemo-immunotherapy in routine clinical practice. While direct comparison with clinical trial health-related quality of life data and AE data is not possible due to differences in study designs, our results suggest broadly comparable health-related quality of life, but higher than expected symptom burden compared to AEs reported in published trials. Dermatologic symptoms, cough, arthralgia, myalgia, and financial concerns were more prevalent than expected and may warrant heightened attention in clinical practice. These differences may reflect a sample that was more heavily pre-treated and had lower socioeconomic status, more non-cancer comorbidities, and worse PS. Closer monitoring of health-related quality of life and symptom burden also may be needed in clinical practice for patients with PS 2 or higher. Future trials should include patient-reported outcome measures that better capture dermatologic symptoms and inquire further about financial concerns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- These data are some of the first to describe health related quality of life and symptom experiences of patients receiving immunotherapy or chemo-immunotherapy for metastatic NSCLC in clinical practice. These data are also some of the first to describe patient reports of some symptoms such as rash.
- Though study design precludes attributing symptoms to treatment, disease, or comorbidity, results suggest many patients experience respiratory, gastrointestinal, dermatologic, arthralgia, and myalgia symptoms. Results also suggest fatigue, pain, insomnia, and financial concerns may be a concern for many patients in clinical practice.
- Although patients age 70 and older did not appear to have worse quality of life and symptom experiences compared to those younger than 70, PS 2/3 patients reported worse global health-related quality of life and higher pain compared to PS 0/1 patients.
- Closer monitoring of quality of life and symptom burden may be needed, especially for patients with PS 2 or higher.

Table 1

Sociodemographic and Clinical Characteristics of Patients with Stage IV Non-Small Cell Lung Cancer receiving Immunotherapy with or without Chemotherapy in Routine Clinical Care (N = 60)

Sociodemographics	**n (%)/Mean (SD)**
Age – mean (sd)	62.5 (9.3); Median = 62.5; range 40–82 years
Age ≥70 y.o. –n (%)	15 (25.0)
Race --n (%)	
White	44 (73.3)
Black	11 (18.3)
Asian	1 (1.7)
Other	1(1.7)
Declined to answer	2 (3.3)
Missing	1 (1.7)
Hispanic--n (%)	2 (3.3)
Female – n (%)	36 (60.0)
Currently married--n (%)	39 (65.0)
Rural [a] – n (%)	21 (35.0)
Education—n (%)	
Some HS or less	9 (15.0)
HS diploma	16 (26.7)
Some college	25 (41.7)
College graduate or more	9 (15.0)
Missing	1 (1.7)
Household income--n (%)	
<$25K	23 (38.3)
$25K – 49,999	12 (20.0)
$50K – 99,999	7 (11.7)
≥$100K	7 (11.7)
Missing	11 (18.3)
Current employment status	
Working full time	13 (21.7)
Retired	20 (33.3)
Disabled	20 (33.3)
Other	2 (3.3)
Missing	5 (8.3)
Clinical	
Cigarette pack years—mean (sd)	32.7 (21.1); median 30, range = 1–100
Currently smoking [b] --n (%)	15 (25)
ECOG PS--n (%)	
0	4 (6.7)
1	37 (61.7)

Sociodemographics	n (%)/Mean (SD)
2	17 (28.3)
3	2 (3.3)
De novo stage IV NSCLC--n (%)	47 (78.3)
Current immunotherapy agent--n (%)	
Pembrolizumab	45 (75.0)
Pembro alone --n	19
Carboplatin-Pemetrexed--n	12
Pemetrexed-Pembrolizumab--n	13
Pembrolizumab-carboplatin--n	1
Nivolumab	13 (21.7)
Atezolizumab	2 (3.3)
Weeks on immunotherapy—mean (sd)	29 (31); median 20.8; range = 0 – 143
Other treatments received to date* --n (%)	
Chemotherapy	48 (80.0)
Radiation	20 (33.3)
Concurrent chemo-radiotherapy	3 (5)
Targeted therapy	4 (6.7)
Gamma knife	23 (38.3)
Surgery	17 (28.3)
Whole brain radiotherapy	2 (3.3)
Stereotactic body radiation therapy	5 (8.3)
Craniotomy	11 (18.3)
At least 1 non-cancer comorbidity – n (%)	30 (50.0)
Reimaged for response** --n (%)	
Not yet reimaged	23 (38.3)
Reimaged: Partial/Complete response	11 (18.3)
Reimaged: Stable disease	24 (40.0)
Reimaged: Progressive disease	2 (3.3)

Note. HS = high school; ECOG PS = Eastern Cooperative Oncology Group Performance Status

[a]Rural: Federal Office of Rural Health Policy's eligible ZIP codes (ZIP code with more than 50% of the population residing in a non-metro county or rural census tract included as rural).

[b]Currently smoking = reported smoking a cigarette within the past 7 days;

*Patients could have multiple prior treatments more so percents total to more than 100

**We intentionally sampled patients who had not yet been reimaged to evaluate treatment response to obtain a sample of patients who were earlier vs. later into treatment.

Table 2.

Health-Related Global Quality of Life, Function, and Symptom Scores on the EORTC-QLQ-C30 in Patients with Stage IV Non-Small Cell Lung Cancer receiving Immunotherapy or Chemo-Immunotherapy, Overall and by Performance Status and Age

	Overall Sample (N = 60)	ECOG Performance Status			Age		
Scale	**Mean (SD)**	**PS 0/1 (n = 41)**	**PS 2/3 (n = 19)**	***p***	**Age < 70 (n = 45)**	**Age 70+ (n = 15)**	***p***
Global Health	62.6 (21.5)	67.7 (18.8)	51.8 (23.2)	.006	61.7 (21.1)	65.6 (23.1)	.55
Function Subscales							
Cognitive Function	81.7 (21.0)	81.3 (20.8)	82.5 (21.9)	.84	80.7 (22.2)	84.4 (17.2)	.56
Emotional Function	79.7 (20.1)	79.9 (20.8)	79.4 (18.9)	.93	78.3 (21.4)	83.9 (15.3)	.36
Physical Function	74.5 (20.7)	80.2 (18.6)	62.1 (20.0)	.001	73.7 (21.0)	76.8 (20.4)	.62
Social Function	73.6 (26.3)	74.4 (26.1)	71.9 (27.2)	.74	69.6 (28.0)	85.6 (15.3)	.008
Role Function	70.0 (32.3)	75.6 (30.5)	57.9 (33.5)	.047	70.0 (33.3)	70.0 (30.3)	1.00
Symptom Subscales							
Fatigue	39.6 (28.5)	35.2 (28.6)	49.1 (26.5)	.08	40.2 (27.7)	37.8 (31.9)	.77
Insomnia	37.9 (36.6)	35.04 (35.0)	43.9 (40.1)	.39	40.2 (39.1)	31.0 (27.6)	.42
Dyspnea	35.0 (29.7)	30.9 (28.3)	43.9 (31.5)	.12	34.8 (29.3)	35.6 (32.0)	.93
Financial	32.8 (36.0)	31.7 (37.2)	35.1 (34.2)	.74	37.0 (37.1)	20.0 (30.3)	.11
Pain	28.1 (30.3)	19.9 (26.9)	45.6 (30.3)	.002	28.9 (28.7)	25.6 (35.6)	.72
Appetite	23.3 (31.5)	19.5 (30.7)	31.6 (32.3)	.17	24.4 (33.6)	20.0 (24.6)	.64
Constipation	18.3 (24.9)	19.5 (24.7)	15.8 (25.7)	.59	17.8 (25.2)	20.0 (24.6)	.77
Nausea	11.4 (18.3)	10.6 (18.5)	13.2 (18.1)	.61	14.1 (19.8)	3.3 (9.3)	.007
Diarrhea	8.3 (20.0)	4.9 (14.1)	15.8 (28.0)	.12	10.4 (22.3)	2.2 (8.6)	.046

Note. EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30. ECOG = Eastern Cooperative Oncology Group. Statistical significance was tested with independent samples t-tests.

Table 3.

Number and Proportion of Patients with Stage IV Non-Small Cell Lung Cancer receiving Immunotherapy or Chemo-immunotherapy Endorsing at Least Moderate/Occasional Past Week Symptoms on the NCI-PRO-CTCAE™, Overall and by Performance Status and Age

	Overall Sample (N = 60)	ECOG Performance Status			Age		
Past Week Symptoms – NCI PRO-CTCAE™	**n (%) At Least Moderate/ Occasional Symptom**	**PS 0/1 (n = 41) n (%)**	**PS 2/3 (n = 19) n (%)**	***p***	**Age < 70 (n = 45) n (%)**	**Age 70+ (n = 15) n (%)**	***p***
Constipation severity	13 (21.7)	8 (19.5)	5 (26.3)	.74	8 (17.8)	5 (33.3)	.28
Diarrhea frequency	11 (18.3)	5 (12.2)	6 (31.6)	.09	9 (20.0)	2 (13.3)	.71
Bowel incontinence frequency	2 (3.3)	2 (4.9)	0 (0)	1.0	2 (4.4)	0 (0)	1.0
Abdominal pain frequency	7 (11.7)	5 (12.2)	2 (10.5)	1.0	7 (15.6)	0 (0)	.18
Fatigue severity	30 (50.0)	20 (48.8)	10 (52.6)	.78	24 (53.3)	6 (40.0)	.37
Pain frequency	25 (41.7)	12 (29.3)	13 (68.4)	.004	19 (42.2)	6 (40.0)	.88
Cough severity	15 (25.0)	7 (17.1)	8 (42.1)	.06	12 (26.7)	3 (20.0)	.74
Wheezing severity	7 (11.7)	5 (12.2)	2 (10.5)	1.0	7 (15.6)	0 (0)	.18
Shortness of breath severity	14 (23.3)	9 (22.0)	5 (26.3)	.75	10 (22.2)	4 (26.7)	.74
Rash (yes/no)	16 (26.7)	12 (29.3)	4 (21.1)	.50	13 (28.9)	3 (20.0)	.74
Dry skin severity	12 (20.7)	7 (18.0)	5 (26.3)	.50	11 (25.0)	1 (7.1)	.26
Itchy skin severity	13 (22.4)	8 (20.5)	5 (26.3)	.74	11 (25.6)	2 (13.3)	.48
Muscle ache frequency	24 (40.0)	18 (43.9)	6 (31.6)	.36	20 (44.4)	4 (26.7)	.22
Joint pain frequency	20 (33.3)	11 (26.8)	9 (47.4)	.12	16 (35.6)	4 (26.7)	.53
Decreased appetite severity	14 (23.3)	7 (17.1)	7 (36.8)	.11	11 (24.4)	3 (20.0)	1.0
Arm or leg swelling severity	7 (11.7)	5 (12.2)	2 (10.5)	1.0	7 (15.6)	0 (0)	.18
Nausea frequency	10 (16.7)	7 (17.1)	3 (15.8)	1.0	9 (20.0)	1 (6.7)	.43

Note. NCI-PRO-CTCAE™ = National Cancer Institute Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events-. Statistical significance was tested with chi-square or Fisher's exact tests.