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Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: https://www.tandfonline.com/loi/ijme20

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To cite this article: Karen E. Skinner, Ancilla W. Fernandes, Mark S. Walker, Melissa Pavilack & Ari VanderWalde (2018) Healthcare costs in patients with advanced non-small cell lung cancer and disease progression during targeted therapy: a real-world observational study, Journal of Medical Economics, 21:2, 192-200, DOI: 10.1080/13696998.2017.1389744

To link to this article: https://doi.org/10.1080/13696998.2017.1389744

Published online: 18 Oct 2017.

JOURNAL OF MEDICAL ECONOMICS, 2018
VOL. 21, NO. 2, 192–200
https://doi.org/10.1080/13696998.2017.1389744
Article 0145-RT.R1/1389744

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ORIGINAL RESEARCH

Healthcare costs in patients with advanced non-small cell lung cancer and disease progression during targeted therapy: a real-world observational study

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ABSTRACT

Aims: To assess healthcare costs during treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and following disease progression in patients with advanced non-small cell lung cancer (NSCLC).

Methods: A retrospective analysis of medical records of US community oncology practices was conducted. Eligible patients had advanced NSCLC (stage IIIB/IV) diagnosed between January 1, 2008 and January 1, 2015, initiated treatment with erlotinib or afatinib (first-line or second-line), and had disease progression. Monthly Medicare-paid costs were evaluated during the TKI therapy period and following progression.

Results: The study included 364 patients. The total mean monthly cost during TKI therapy was $20,106 (95% confidence interval [CI] = $16,836–$23,376), of which 47.0% and 42.4% represented hospitalization costs and anti-cancer therapy costs, respectively. Following progression on TKI therapy (data available for 316 patients), total mean monthly cost was $19,274 (95% CI = $15,329–$23,218), and was higher in the 76.3% of patients who received anti-cancer therapy following progression than in the 23.7% of those who did not ($20,490 vs $15,364; $p < .001$). Among patients who received it, anti-cancer therapy ($11,198; 95% CI = $7,102–$15,295) represented 54.7% of total mean monthly cost. Among patients who did not receive anti-cancer therapy, hospitalization ($13,829; 95% CI = $4,922–$22,736) represented 90.0% of total mean monthly cost. Impaired performance status and brain metastases were significant predictors of increased cost during TKI therapy.

Limitations: The study design may limit the generalizability of findings.

Conclusions: Healthcare costs during TKI treatment and following progression appeared to be similar and were largely attributed to hospitalization and anti-cancer therapy. Notably, almost one-quarter of patients did not receive anti-cancer therapy following progression, potentially indicating an unmet need; hospitalization was the largest cost contributor for these patients. Additional effective targeted therapies are needed that could prolong progression-free survival, leading to fewer hospitalizations for EGFR mutation-positive patients.

ARTICLE HISTORY
Received 8 August 2017
Revised 2 October 2017
Accepted 5 October 2017

KEYWORDS
Advanced NSCLC; community oncology; healthcare resource utilization; cost

Introduction

Lung and bronchial cancers are the third costliest cancers to treat in the US[1–3], and are also the leading cause of cancer death, with only 18% of all patients alive 5 years after diagnosis[2,4]. Globally, ~2 million incident cases of tracheal, bronchus, and lung cancer were diagnosed in 2015 and 1.7 million patients with tracheal, bronchus, and lung cancer died the same year[5]. Non-small cell lung cancer (NSCLC) accounts for ~80% of incident lung cancer cases[2], with ~50% of patients having stage IV disease at initial diagnosis[6]. The high cost of care and poor long-term prognosis highlight the need to balance patient access to best treatment with healthcare sustainability and societal burden, particularly in the advanced disease setting[7].

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) provide targeted treatment for EGFR-mutation (EGFRm)-positive NSCLC. Results from phase 2 studies and phase 3 randomized, controlled trials demonstrate superior progression-free survival (PFS), higher objective responses, and favorable safety profiles with the TKIs erlotinib, gefitinib, and afatinib compared with standard first-line platinum-based doublet chemotherapy in patients with EGFRm-positive NSCLC[8–18]. A recent review indicated a median progression-free survival (PFS) of 8–13 months for patients with EGFRm-positive NSCLC receiving first-line EGFR TKIs[19]. In contrast, median time to progression or PFS for patients receiving platinum-based doublet chemotherapy combinations was 4–6 months[20–23].

The National Comprehensive Cancer Network (NCCN) guidelines recommend first-line therapy with an approved TKI for treatment of EGFRm-positive NSCLC[4]. The guidelines recommend continued TKI therapy after disease progression right up until switching to the next line of therapy[4].

Research that evaluates the cost of care in patients with advanced NSCLC and disease progression in the real world is limited. A study by Fox *et al.*[24] evaluated healthcare costs in

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patients with advanced NSCLC who were treated with chemotherapy. A comparison of costs of care in the 3 months after progression among patients with disease progression with the same time period among patients without disease progression showed that costs were significantly higher for patients with disease progression than for those without progression. However, the study did not evaluate the cost of care for patients with advanced NSCLC who were treated with agents other than chemotherapy, which may limit the generalizability of these findings.

A cursory review of the literature did not identify any studies that assessed the burden and components of cost during TKI treatment and following disease progression on TKIs. Given the growing need for cost containment, characterizing healthcare cost is necessary to understand the economic burden among patients receiving EGFR TKIs during first-line or second-line therapy and following subsequent disease progression. Examination of cost could include evaluation of cost components, which might help to identify areas of under-utilization[25]. In this retrospective observational study in the community oncology setting, we investigated healthcare utilization costs in patients with advanced NSCLC who initiated TKI therapy and experienced disease progression.

Methods

Data source

This was a retrospective observational study. Electronic medical record (EMR) and billing data were obtained from the Vector Oncology Data Warehouse, which is a repository of data from 10 community oncology practices in the US. The Vector Oncology Data Warehouse includes provider notes to support collection of key information, such as verification of EGFR testing and confirmation of patient treatment, that is not routinely available in the pre-specified EMR data-entry fields. The study protocol was approved by IntegReview Institutional Review Board.

Patients

To be included in this analysis, patients needed to be aged 18 years or older and to have received a diagnosis of advanced NSCLC between January 1, 2008 and January 1, 2015 (study inclusion period). Advanced NSCLC was defined as either an initial diagnosis of stage IIIB or stage IV disease, or earlier stage disease that had since recurred regionally or become metastatic. Patients were either diagnosed initially as advanced, or had progressed to advanced disease prior to inclusion in the analysis. In addition, patients needed to have been treated with either erlotinib or afatinib, as first-line or second-line therapy following diagnosis of advanced NSCLC, and to have experienced disease progression, as assessed by the treating clinician, before October 31, 2015 (the end of follow-up).

Patients were excluded from this study if they were treated with osimertinib (which was approved after the study period). Patients were also excluded if they had received afatinib before it had been approved (July 2013) or if they had received gefitinib (which was reapproved after the study period).

Data collection

Basic demographic and clinical characteristics were assessed. Demographics included insurance status, age, sex, and race, which, together with admitting diagnosis and length of hospital stay, were used to enable matching of hospitalization events to the National (Nationwide) Inpatient Sample (NIS), which is part of the Healthcare Cost and Utilization Project (HCUP). Clinical characteristics that were obtained included performance status (Eastern Cooperative Oncology Group performance status, or provider documented impairment), histology, metastatic disease sites, EGFRm status, comorbid conditions, and smoking history. The occurrence of disease progression was determined from pathology reports, radiological scans, lab values, or provider progress notes. Healthcare Common Procedure Coding System/Current Procedural Terminology (HCPCS/CPT) codes were collected from the EMR data for outpatient procedures and physician office visits.

As described above, EGFRm status was documented as available for each patient. It is important to note that erlotinib was approved independent of EGFRm status for most of the study period. Erlotinib was not approved specifically for EGFRm positive patients until 2013. Thus, testing was not uniformly done prior to this date.

Assessment of healthcare cost

Medicare-paid costs were evaluated for the following two time periods: (1) the time period from the start of initial TKI therapy to disease progression (TKI treatment period) and (2) the time period following disease progression on TKIs (the post-disease progression period). Cost reflects the average negotiated allowed amount for each cost component. All patients were followed up from the start of TKI treatment through to the end of the line of treatment following disease progression on TKIs, or until the end of the record, whichever

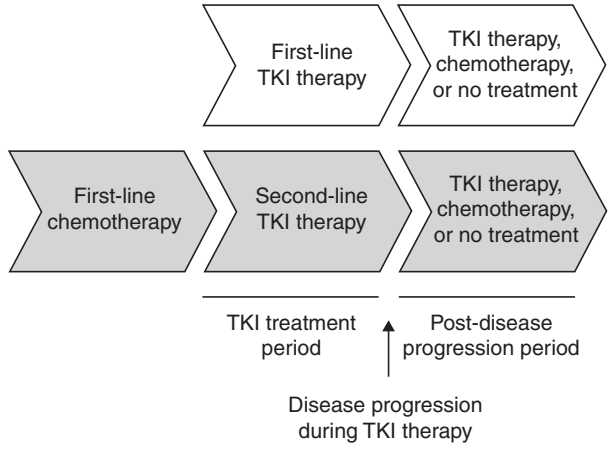


Figure 1. Flow chart showing the two separate patient groups and study time periods. Abbreviation. TKI, tyrosine kinase inhibitor.

occurred first. Costs were evaluated separately for patients who initiated TKIs as first-line therapy and those who initiated TKIs as second-line therapy (Figure 1).

Healthcare costs were evaluated on a per month basis to adjust for variable durations of the treatment/progression period. Total monthly costs comprised all expenditures associated with inpatient hospitalization, physician office visits, infused supportive care drugs, systemic anti-cancer therapy, all other drugs provided, and procedures delivered in the medical oncology setting. In addition, mean overall (i.e. not monthly) total costs were evaluated separately for the TKI treatment period and for the post disease-progression period for descriptive purposes.

Hospitalization costs were estimated based on the median cost of case-matched hospitalizations for patients with cancer in the HCUP NIS[26]. Diagnoses, length of stay, age range, sex, and race were used as key match criteria. Costs for outpatient procedures and physician office visits were estimated by matching patients' HCPCS/CPT codes from the EMR data to published national median paid amounts listed in the Centers for Medicare and Medicaid Services fee schedule. The mean wholesale price reported in Red Book was used to determine the cost for each medication. Costs incurred in the year 2016 were unadjusted. However, costs incurred prior to year 2016 were adjusted to the year 2016 price value using inflation rates from the US consumer price index[27–29].

Statistical methods

The overall cost of care for each treatment period was defined as the sum of the following individual cost components: hospitalizations, physician office visits, procedures, systemic anti-cancer therapy, infused supportive care, and other drugs. The monthly cost of care in each period was defined as the overall cost divided by the total duration of the covered period, in months. Analyses of monthly costs were conducted separately for total monthly costs and individual cost components. Unadjusted pairwise comparisons for first-line vs second-line therapy were performed using a *t*-test on log-transformed costs, assuming an underlying distribution of cost data that is skewed to the right. Adjusted comparisons between groups initiating TKIs as first-line vs second-line therapy used generalized linear regression models with a log-link function and γ distribution, controlling for demographic and clinical characteristics. For the post-disease progression period, total monthly costs and individual cost components were compared between patients who received systemic anti-cancer therapy in the post-progression period and those who did not.

Results

Patients

Of 364 patients with advanced NSCLC who were included in the analysis, 233 initiated TKIs as first-line therapy and 131 as second-line therapy. Table 1 shows demographic and clinical characteristics for the two patient groups. Overall, the mean age was 66.3 years, 51.6% of patients were women, and 68.4% of patients had stage IV disease at the time of diagnosis.

EGFRm testing rates ("ever tested") were higher in the group that initiated TKI as first-line therapy than in the group that initiated it as second-line therapy (54.5% were tested before receiving vs 35.1%, $p < .001$). The pattern of results suggests that patients who initiated TKI as first-line therapy may have been more likely to be EGFRm positive, although pairwise testing was not conducted.

The proportion of patients with impaired performance status was 11.0% overall, and did not differ significantly between the group that initiated TKIs as first-line therapy and the group that initiated TKIs as second-line therapy. Patients who initiated TKIs as second-line therapy tended to be more likely to have at least one comorbid condition than those initiating TKIs as first-line therapy (60.3% vs 49.8%, $p = .063$).

Monthly healthcare costs during the TKI treatment period

The components of monthly healthcare cost during the TKI treatment period are presented in Figure 2. The total mean monthly cost (i.e. the sum of the individual components) during the TKI treatment period was $20,106 (95% confidence interval [CI] = $16,836–$23,376). The monthly cost during this period was lower in patients who initiated TKIs as first-line therapy than in those who initiated treatment as second-line therapy ($18,354 [95% CI = $13,929–$22,781] vs $23,221 [95% CI = $18,660–$27,782]; $p = .002$).

During the TKI treatment period, close to half of the total mean monthly cost was attributed to hospitalizations (47.0%; $9,454 [95% CI = $6,551–$12,358]). The cost of systemic anti-cancer therapy represented an additional 42.4% of the total mean monthly cost ($8,530 [95% CI = $7,141–$9,919]). The mean monthly costs of hospitalization and systemic anti-cancer therapy did not differ significantly between patients who initiated TKIs as first-line therapy and those who initiated treatment as second-line therapy (Figure 2).

The multivariate model showed that key drivers of the total mean monthly cost were the presence of brain metastases and impaired performance status (data not shown). Patients with brain metastases and those with impaired performance status incurred higher monthly costs during the TKI treatment period than those without (linear regression model, $p = .046$ and $p < .001$, respectively). The total mean overall cost of healthcare for the entire TKI treatment period was $147,985 (95% CI = $124,573–$171,397).

Monthly healthcare costs during the post-disease progression period

Data for cost analysis in the post-disease progression period were available for 316 patients, of whom 208 had initiated TKIs as first-line therapy and 108 as second-line therapy. The total mean monthly cost during the post-disease progression period was $19,274 (95% CI = $15,329–$23,218). The total

Table 1. Demographic and clinical characteristics of patients with advanced NSCLC who initiated TKIs as first-line therapy or as second-line therapy.

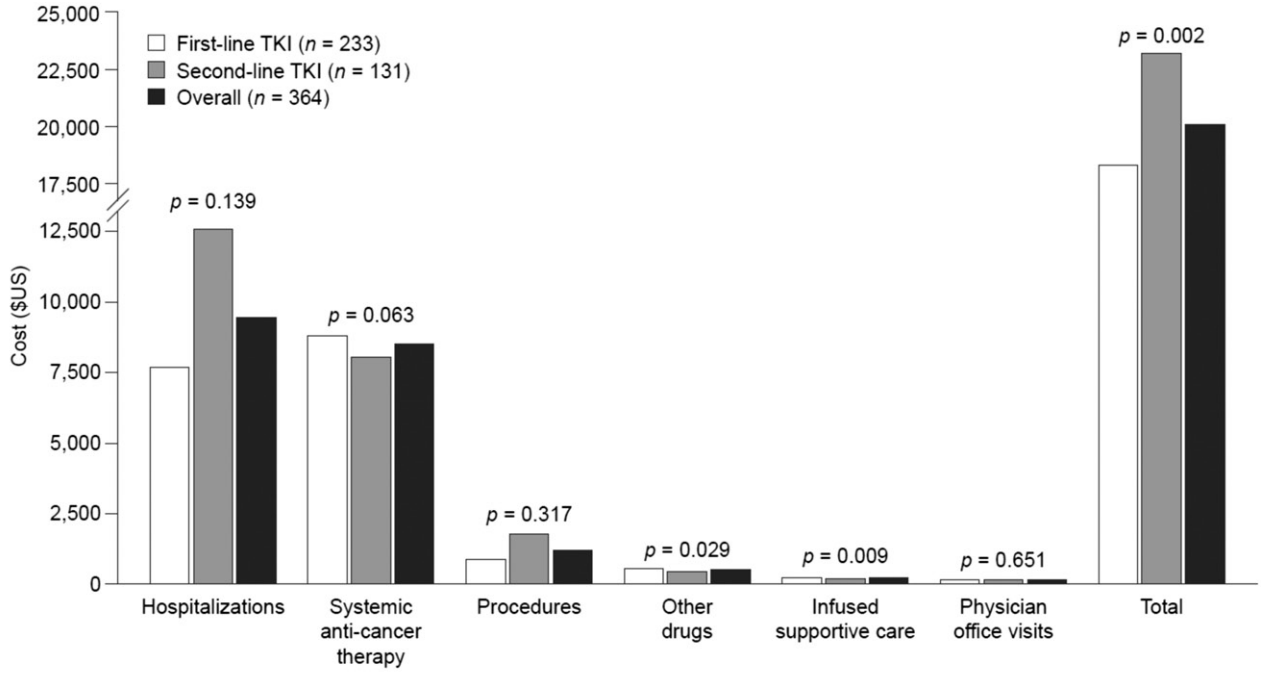
Characteristic	First-line TKI ($n = 233$)	Second-line TKI ($n = 131$)	Overall ($n = 364$)	p-value[a]
Age, years, mean (SD)[b]	67.0 (12.10)	65.1 (9.64)	66.3 (11.30)	.132[c]
Female, *n* (%)	127 (54.5)	61 (46.6)	188 (51.6)	.156
Race, *n* (%)				.231
Asian	6 (2.6)	0	6 (1.6)	
Black or African-American	42 (18.0)	21 (16.0)	63 (17.3)	
Hispanic or Latino	0 (0.0)	1 (0.8)	1 (0.3)	
White	178 (76.4)	105 (80.2)	283 (77.7)	
Not documented	7 (3.0)	4 (3.1)	11 (3.0)	
BMI, kg/m^2, mean (SD)[b,d]	26.2 (5.6)	26.6 (6.0)	26.4 (5.7)	.541[c]
Type of health insurance, *n* (%)				.464
Private and public	94 (40.3)	55 (42.0)	149 (40.9)	
Private only	48 (20.6)	27 (20.6)	75 (20.6)	
Public only	65 (27.9)	37 (28.2)	102 (28.0)	
Neither private nor public	9 (3.9)	8 (6.1)	17 (4.7)	
Not documented	17 (7.3)	4 (3.1)	21 (5.8)	
Stage of disease at initial diagnosis, *n* (%)				.011
Stage 0/I	21 (9.0)	3 (2.3)	24 (6.6)	
Stage II	13 (5.6)	2 (1.5)	15 (4.1)	
Stage III	37 (15.9)	29 (22.1)	66 (18.1)	
Stage IV	154 (66.1)	95 (72.5)	249 (68.4)	
Not documented	8 (3.4)	2 (1.5)	10 (2.7)	
Disease histology, *n* (%)				
Adenocarcinoma	179 (76.8)	76 (58.0)	255 (70.1)	<.001
NSCLC not otherwise specified	8 (3.4)	13 (9.9)	21 (5.8)	.017
Other	8 (3.4)	8 (6.1)	16 (4.4)	.288
Squamous cell carcinoma	36 (15.5)	33 (25.2)	69 (19.0)	.026
Undocumented	3 (1.3)	1 (0.8)	4 (1.1)	>.999
Site(s) of distant metastases, *n* (%)[b]				
Bone	75 (32.2)	33 (25.2)	108 (29.7)	.189
Brain	53 (22.7)	30 (22.9)	83 (22.8)	>.999
Contralateral lung	66 (28.3)	49 (37.4)	115 (31.6)	.079
Other	99 (42.5)	52 (39.7)	151 (41.5)	.658
EGFR mutation status, *n* (%)				
Ever tested	127 (54.5)	46 (35.1)	173 (47.5)	<.001
At TKI initiation[e]				<.001
Positive	73 (31.3)	11 (8.4)	84 (23.1)	
Negative	34 (14.6)	31 (23.7)	65 (17.9)	
Undocumented	126 (54.1)	89 (67.9)	215 (59.1)	
Impaired performance status, *n* (%)[b]	30 (12.9)	10 (7.6)	40 (11.0)	.162
Any comorbid condition, *n* (%)	116 (49.8)	79 (60.3)	195 (53.6)	.063
Smoking/tobacco use status, *n* (%)[b]				<.001
Current/past	160 (68.7)	119 (90.8)	195 (53.6)	
Never	73 (31.3)	12 (9.2)	85 (23.4)	

Abbreviations. BMI, body mass index; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SD, standard deviation; TKI, tyrosine kinase inhibitor.
[a]χ^2 or Fisher's exact test were used unless otherwise indicated. p-values refer to comparisons between first-line and second-line TKI therapy initiation groups.
[b]At diagnosis of advanced NSCLC.
[c]Independent samples t-test or non-parametric equivalent was used.
[d]BMI data were unavailable for four patients in the group who initiated TKI as first-line therapy.
[e]Mutation testing conducted within ±30 days of TKI therapy initiation.

mean monthly cost during this period was lower in patients who initiated TKI as second-line therapy than in those who initiated TKI as first-line therapy (first-line vs second-line: $21,930 [95% CI = $16,399–$27,460] vs 14,158 [95% CI = $9,757–$18,560]; $p = .011$). The higher total mean monthly cost in patients who initiated TKIs as first-line therapy than in those who initiated TKIs as second-line therapy is probably due to higher systemic anti-cancer therapy costs in the first-line than the second-line group ($10,355 [$5,862–$14,848] vs $5,045 [95% CI = $1,763–$8,328]; $p = .011$). However, in the multivariate model, line of TKI initiation was not a significant predictor of monthly cost.

Nearly one-quarter (23.7% [75/316]) of patients with evaluable cost data for the post-disease progression period received no systemic anti-cancer therapy following their disease progression. Of patients who initiated TKIs as second-line therapy, 29.6% did not receive systemic anti-cancer therapy in the post-disease progression period, compared with 20.7% of patients who initiated TKIs as first-line therapy. Of the 76.3% (241/316) of patients who did receive further systemic anti-cancer treatment following disease progression, 33.2% (80/241) continued with TKI therapy, either as monotherapy or in combination with other agents, and 66.8% of patients (161/241) switched to chemotherapy.

Table 2 shows demographic and clinical characteristics separately for the 241 patients who received systemic anti-cancer therapy during the post-disease progression period and the 75 patients who did not receive such therapy. The characteristics generally did not differ between the two groups. However, compared with untreated patients, those who received anti-cancer therapy were more likely to have



	Hospitalizations	Systemic anti-cancer therapy	Procedures	Other drugs	Infused supportive care	Physician office visits	Total
First-line TKI	$7,699	$8,794	$896	$556	$251	$158	$18,354
Second-line TKI	$12,577	$8,060	$1,781	$436	$204	$163	$23,221
Overall	$9,454	$8,530	$1,215	$513	$234	$160	$20,106

Figure 2. Mean monthly healthcare costs during the TKI treatment period for patients who initiated TKIs as first-line therapy and those who initiated it as second-line therapy. Abbreviation. TKI, tyrosine kinase inhibitor. *p*-values refer to comparisons of first-line and second-line TKI groups.

adenocarcinoma (57.3% vs 74.7%; $p = .006$), to have been tested for EGFRm (33.3% vs 53.1%; $p = .004$), and were less likely to have a history of smoking (92.0% vs 72.2%; $p < .001$).

The components of the monthly cost during the post-disease progression period for patients who received systemic anti-cancer therapy in the post-disease progression period and those who did not receive such therapy are presented in Figure 3. The total mean monthly cost of healthcare in the post-disease progression period was higher in patients who received systemic anti-cancer therapy than in those who did not ($20,490 [95% CI = $16,111–$24,870] vs $15,364 [$6,384–$24,344]; $p < .001$). Costs differed significantly between treatment groups for all cost components, except for hospitalizations (Figure 3). For patients who received systemic anti-cancer therapy, the cost of this therapy represented the greatest proportion of the total mean monthly cost (54.6%, $11,198 [95% CI = $7,102–$15,295]). For patients who did not receive systemic anti-cancer therapy (and who, thus, did not incur any cost for such therapy), the greatest proportion of the total mean monthly cost was attributed to hospitalizations (90.0%, $13,829 [95% CI = $4,922–$22,736]).

The multivariate model showed that, unlike during the TKI treatment period, in the post-disease progression period impaired performance status and brain metastases were not key drivers of total mean monthly cost (data not shown). The data showed that impaired performance status was not a significant predictor of cost of care ($p = .614$) and presence of brain metastases was associated with lower monthly costs ($p = .024$). The percentage of patients with brain metastases at the start of the post-disease progression period was higher in the group who did not receive systemic anti-cancer therapy in the post-disease progression period than in the group who did receive such therapy (38.7% vs 24.9%; $p = .027$), which could account for the observed association between brain metastases and decreased monthly costs during the post-disease progression period.

The total mean overall cost of care was evaluated descriptively for the entire post-disease progression period, and was $93,105 (95% CI = $64,924–$121,286).

Discussion

This retrospective, real-world study examined the cost of care in patients who initiated TKI therapy for advanced NSCLC. Costs were assessed separately for the TKI treatment period and the post-disease progression period. The study results suggest that total mean monthly costs were similar during the TKI treatment and post-disease progression periods ($20,106 vs $19,274, respectively). In both periods, hospitalizations and systemic anti-cancer therapy together accounted for ~85–90% of the total mean monthly cost. The remaining 10–15% in each period was attributed to a combination of physician office visits, procedures, infused supportive care drugs, and other drugs. Impaired performance status and brain metastases were key drivers of an increased total monthly cost during the TKI treatment period, but not after disease progression.

Of the 316 patients for whom post-disease progression cost data were available, a substantial proportion (23.7% [75/

Table 2. Demographic and clinical characteristics of patients who received systemic anti-cancer therapy in the post-disease progression period and those who did not receive such therapy.

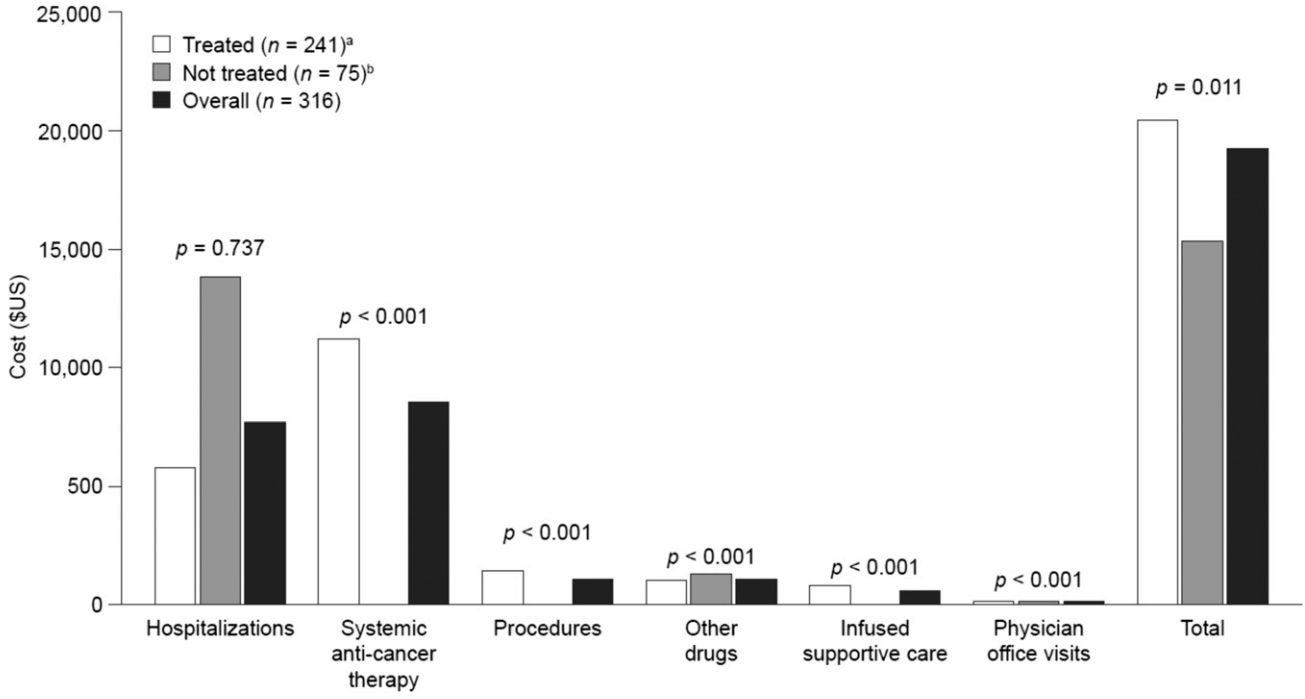
Characteristic	Treated[a] ($n = 241$)	Not treated[b] ($n = 75$)	Overall ($n = 316$)	p-value
Age, years, mean (SD)[c]	65.6 (11.2)	67.0 (11.6)	66.0 (11.3)	.377[d]
Female, *n* (%)	129 (53.5)	32 (42.7)	161 (50.9)	.113[e]
Race, *n* (%)				.818[e]
Asian	5 (2.1)	1 (1.3)	6 (1.9)	
Black or African-American	47 (19.5)	11 (14.7)	58 (18.4)	
White	182 (75.5)	61 (81.3)	243 (76.9)	
Not documented	7 (2.9)	2 (2.7)	9 (2.8)	
BMI, kg/m^2, mean (SD)[c]	26.6 (5.7)	26.6 (6.0)	26.4 (5.7)	.533[d]
Type of health insurance, *n* (%)				.3216[e]
Private and public	98 (40.7)	28 (37.3)	126 (39.9)	
Private only	56 (23.2)	11 (14.7%)	67 (21.2)	
Public only	62 (25.7)	26 (34.7)	88 (27.8)	
Neither private nor public	12 (5.0)	4 (5.3)	16 (5.1)	
Not documented	13 (5.4)	6 (8.0)	19 (6.0)	
Stage of disease at initial diagnosis, *n* (%)				.106[e]
Stage 0/I	18 (7.5)	4 (5.3)	22 (7.0)	
Stage II	12 (5.0)	1 (1.3)	13 (4.1)	
Stage III	36 (14.9)	19 (25.3)	55 (17.4)	
Stage IV	169 (70.1)	47 (62.7)	216 (68.4)	
Not documented	6 (2.5)	4 (5.3)	10 (3.2)	
Disease histology, *n* (%)				
Adenocarcinoma	180 (74.7)	43 (57.3)	223 (70.6)	.006[e]
NSCLC not otherwise specified	8 (3.3)	10 (13.3)	18 (5.7)	.003[e]
Site(s) of distant metastases at start of post-progression period, *n* (%)				
Bone	92 (38.2)	18 (24.0)	110 (34.8)	.027[e]
Brain	60 (24.9)	29 (38.7)	89 (28.2)	.027[e]
Contralateral lung	84 (34.9)	31 (41.3)	115 (36.4)	.337[e]
Liver	50 (20.7)	16 (21.3)	66 (20.9)	>.999[e]
EGFR mutation status, *n* (%)				
Ever tested	128 (53.1)	25 (33.3)	153 (48.4)	.004[e]
At start of post-progression period[f]				.875[e]
Positive	20 (8.3)	7 (9.3)	27 (8.5)	
Negative	13 (5.4)	3 (4.0)	16 (5.1)	
Undocumented	208 (86.3)	65 (86.7)	273 (86.4)	
Impaired performance status, *n* (%)[c]	70 (29.0)	16 (21.3)	86 (27.2)	.235[e]
Any comorbid condition, *n* (%)	116 (48.1)	49 (65.3)	195 (56.4)	.012[e]
Smoking/tobacco use status, *n* (%)[c]				<.001[e]
Current/past	174 (72.2)	69 (92.0)	243 (76.9)	
Never	67 (27.8)	6 (8.0)	73 (23.1)	

Abbreviations. BMI, body mass index; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SD, standard deviation; TKI, tyrosine kinase inhibitor.
[a]Patients who received TKI or chemotherapy alone or in combination in the post-disease progression period.
[b]Patients who did not receive any systemic anti-cancer therapy in the post-disease progression period.
[c]At diagnosis of advanced NSCLC.
[d]Independent samples *t*-test or non-parametric equivalent.
[e]χ^2 or Fisher's exact test for categorical variables.
[f]Mutation testing conducted within ±30 days of therapy initiation.
p-values refer to comparisons between treated and not treated groups. Treated refers to treated with systemic anti-cancer therapy.

316]) received no further anti-cancer treatment after disease progression on TKI therapy. The mean monthly cost in the post-disease progression period was significantly lower for patients who did not receive any further systemic anti-cancer therapy than for those who did receive such therapy ($15,364 vs $20,490; $p < .001$). Although examining the characteristics of untreated patients was not a pre-defined aim of this study and was, thus, not part of the design, the identified unmet need was subsequently explored. The study data suggest that untreated patients were in poorer health than their treated counterparts, as indicated by the higher likelihood of brain metastases being present in untreated than in treated patients.

To our knowledge, this is the first real-world study to evaluate healthcare costs in patients with advanced NSCLC who initiated TKI as first-line or second-line therapy and experienced disease progression. An earlier study by Fox *et al.*[24], conducted between January 2001 and March 2006, evaluated the real-world cost burden of disease progression in patients with advanced NSCLC with disease progression following first-line chemotherapy. That study included 306 patients receiving chemotherapy, of whom ~8% were prescribed gefitinib as part of second- or third-line therapy. Fox *et al.*[24] demonstrated that the total cost of healthcare for the 3-month period following disease progression on chemotherapy was $31,129 (i.e. roughly $10,400 per month). The current study, conducted between January 2008 and October 2015, adds to the findings by Fox *et al.*[24] by examining the cost of treatment in the post-disease progression period more specifically among patients with disease progression during TKI therapy.

When evaluating total mean overall (i.e. not monthly) cost, the length of PFS is relevant, because longer PFS may be accompanied by increased time on therapy and, therefore,



	Hospitalizations	Systemic anti-cancer therapy	Procedures	Other drugs	Infused supportive care	Physician office visits	Total
Treated	$5,805	$11,198	$1,442	$1,049	$814	$182	$20,490
Not treated	$13,829	$0	$38	$1,320	$12	$165	$15,364
Overall	$7,710	$8,540	$1,109	$1,113	$623	$178	$19,274

Figure 3. Mean monthly healthcare costs during the post-progression period for patients who received systemic anti-cancer therapy in the post-disease progression period and those who did not receive such therapy. [a]Includes patients who received TKI or chemotherapy alone or in combination in the post-progression period. [b]Includes patients who did not receive any systemic anti-cancer therapy in the post-progression period. Abbreviation. TKI, tyrosine kinase inhibitor. *p*-values refer to comparisons of treated and not treated groups.

increased costs during the period of interest. This does indeed appear to be the case: in a separate analysis from the same study population, median PFS was shown to be 4.9 months during the TKI treatment period and 2.7 months in the post-disease progression period[30]. Additionally, the overall PFS during the TKI treatment period (4.9 months) was notably shorter than that observed for a sub-set of patients with EGFRm-positive disease, which was 8.3 months, a value that appears to fall within the limits of previous clinical research[19]. Separately, PFS during the TKI treatment period was longer for patients who initiated TKI as first-line therapy than those who initiated TKI as second-line therapy (6.7 months vs 2.9 months, $p < .001$)[30]. Taken together with the current analysis, total mean overall cost in each period appeared broadly proportional to PFS.

As discussed previously, mean monthly cost was lower in patients who initiated TKI as first-line therapy than those who initiated treatment as second-line therapy ($18,354 vs $23,221, $p = .002$). When evaluating this finding, it is important to consider that patients who initiated TKI as second-line therapy have progressive disease and are logically more likely to incur greater costs than first-line patients.

This study identified several areas worthy of further research, including additional exploration of the dimensions of unmet need among patients with NSCLC and disease progression on TKI therapy. As already noted, we observed that a large proportion of patients did not receive systemic anti-cancer therapy following disease progression and showed that such individuals appeared to be more likely to have brain metastases. Notably, although these patients did not receive systemic anti-cancer therapy, they did incur costs for other facets of care provided by their treating oncologist. Future research should examine whether there are other ways that untreated patients differ from those who receive continued therapy, and should seek to identify new therapeutic management strategies for vulnerable patients[31]. A further area for future research includes evaluation of the overall economic burden experienced by these patients. This topic could be explored by assessing healthcare cost from diagnosis until death and examining changes in costs incurred over the course of patient care. Although our study examined the cost of care in the post-disease progression period, it did not specifically evaluate the cost of the progression event itself, nor the specific costs of end of life care, whether in a hospice or not. Future research on this topic could consider whether cost savings that have been attributed to non-progression are truly about avoided costs, rather than merely about delayed costs.

This study had some important limitations. Our sample comprised patients receiving care in community oncology practices. Costs incurred in these patients thus may not reflect costs incurred in other treatment settings. The Vector Oncology Data Warehouse includes access to both structured data fields as well as the full record including provider progress notes. Data pertaining to oncology care are largely complete. However, there are some exceptions. If a patient becomes ill

during travel and receives care in another state, such out-of-practice care might not be fully captured in our data. Such occurrences are believed to be rare. The generalizability of findings from this study may be limited in other ways. Specifically, the study inclusion criteria required disease progression and treatment with TKI therapy before disease progression. Cost data following progression were not available for 48 patients. Some of these patients may have died shortly after progression, or they may have transferred to a hospice, an event that is not captured in the community oncology data. As a result, costs associated with end of life care may be underrepresented. Additionally, the cost presented in this study reflects the negotiated allowed payment amounts for facilities, providers, and drugs. This method approximates paid amounts, but these are not the actual paid amounts as those vary based on insurers and their proprietary financial arrangements with facilities, provider practices, and drug manufacturers. Finally, many patients received TKI in either EGFRm-negative settings and/or as maintenance therapy during this study period. These therapeutic approaches are no longer consistent with NCCN guidelines; therefore, the treatment patterns observed in this study population may differ from those prevalent in current practice.

Conclusions

This study's examination of the healthcare cost patterns in patients who initiated TKI therapy for advanced NSCLC has identified the economic implications of the healthcare received, which was largely attributed to hospitalizations and systemic anti-cancer therapy, both during TKI treatment and post-disease progression. We identified an unmet need, with almost one-quarter of patients not receiving anti-cancer therapy following disease progression on TKI therapy. Among patients not receiving systemic anti-cancer therapy, hospitalization was the largest cost contributor, highlighting the need for additional effective targeted therapies that could prolong progression-free survival, leading to fewer hospitalizations on or after first- or second-generation EGFR TKIs.

Transparency

Declaration of funding

The study was funded by AstraZeneca.

Declaration of financial/other relationships

AWF and MP are employees of, and own stock in, AstraZeneca. AVW has served as a consultant to AstraZeneca, Bristol-Myers Squibb, Amgen, and Caris Life Sciences, and is an employee of West Cancer Center, through which he has received research funding from Amgen, AstraZeneca, Bristol-Myers Squibb, Roche-Genentech, Merck, Lilly, Millennium, and Polynoma. KES and MSW report no conflicts of interest. JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

The authors would like to thank Carole Chrvala, PhD, of Health Matters, Inc., and Anja Becher, PhD, of Oxford PharmaGenesis, Oxford, UK, for providing medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines and funded by AstraZeneca (Wilmington, DE).

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