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Cost-Utility Analysis of Treatments for Advanced Non-Small Cell Lung Cancer

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Patients who have non-small cell lung cancer (NSCLC) have been resistant to improvements in survival and quality of life from treatment with chemotherapeutic agents. New combination agents and biologics have provided some gains—but at a very high cost.[1] Literature lacks consensus regarding the cost-effectiveness of the new therapeutic biologic agents.[2] Patients and payers therefore face difficult treatment and resource allocation choices, and they require better information about the economic and health consequences of their actions.

An important issue is whether treatment effectiveness continues into the seventh, eighth, even ninth decade of life. Clinical trials have shown that chemotherapy is equally efficacious across different age groups of men and women with lung cancer, including populations 70 years or older.[3-13] Evidence-based clinical guidelines on chemotherapy from the National Institutes of Health and other health authorities have no age-restricted recommendations for patients with lung cancer, suggesting that chemotherapy is recommended for patients of all age groups with lung cancer.[5,14-17]

Numerous economic evaluations of treatments for NSCLC have been primarily based on clinical trial outcome data,[18-23] with cost data obtained from various sources, including observational claims data,[20,24] electronic medical record[22] case reports, protocols, national tariffs, and databases.[18,19,21] These studies have not examined the economics of treatments stratified by age group, including elderly patients. Although these studies may have high internal validity, generalizability is limited by the exclusion and inclusion criteria, assumptions about healthcare utilization and costs, and the controlled aspects of trials, such as the attention paid to patients' compliance with treatment protocols. Trials may exclude patients older than 80 years and those who have difficulty completing the study protocol due to comorbidities and/or difficulty conversing in English. Population-based observational studies indicate whether treatment efficacy under randomized controlled trials in secondary and tertiary centers translates into effectiveness in the community.[25-28]

ABSTRACT

Objectives: Chemotherapy combinations and biologics have increased the overall survival rate for patients with advanced non-small cell lung cancer (NSCLC), but at a very high cost. We evaluated the effectiveness of chemotherapy/targeted therapy among elderly patients with NSCLC stratified by age groups, and then assessed the cost utility of treatment.

Study Design: Retrospective cohort study.

Methods: SEER (Surveillance, Epidemiology, and End Results) program- and Medicare-linked data were used to estimate the total healthcare cost, life-years, and quality-adjusted life-years (QALYs) for elderly (aged 65-94 years) stage IIIB/IV NSCLC patients diagnosed between 2006 and 2009. Patients were grouped into "no chemotherapy," "platinum-based chemotherapy," and "platinum + targeted therapy" cohorts, and propensity score matching was performed. Cost-effectiveness was evaluated with the incremental cost-effectiveness ratio (ICER) and net monetary benefit. Uncertainty was accounted for by presenting cost-effectiveness acceptability curves (CEACs). A 3% discounting was applied to costs (2014 US$) and effectiveness.

Results: A total of 4884 patients were included in the study, with 1628 in each treatment group. The ICER for platinum-based chemotherapy versus no chemotherapy was $124,645 per QALY gained; for platinum + targeted therapy versus platinum-based chemotherapy, it was $864,327 per QALY gained. Similar results were obtained for alternate scenarios and age groups. The CEAC showed that platinum-based chemotherapy was nearly 100% cost-effective at a willingness-to-pay threshold of $200,000 per QALY, while platinum + targeted therapy was 70% cost-effective at a willingness-to-pay threshold of $1 million per QALY.

Conclusions: Platinum-based chemotherapy may be cost-effective compared with no chemotherapy for the overall elderly population and by age group. However, platinum + targeted therapy was not cost-effective compared with the use of platinum-based therapy alone.

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PRACTICAL IMPLICATIONS

- Targeted therapies, in spite of their high cost, are an increasingly used treatment modality (along with platinum-based chemotherapy) for patients with advanced lung cancer. Our analysis showed that the incremental cost-effectiveness ratio for platinum + targeted therapy was about 9 times the commonly cited United States willingness-to-pay threshold.
- The life-years and quality-adjusted life-years decreased with age, but the cost-effectiveness results were similar to the results for the overall elderly population.

The primary objectives of this paper are to determine: 1) whether the efficacy of chemotherapy observed in controlled clinical trials translates into effectiveness in prolonging survival among community-dwelling patients aged 65 to 94 years with stage IIIb/IV NSCLC, 2) the association between the effectiveness of chemotherapy and advancing age, and 3) the cost-effectiveness of chemotherapy overall and stratified by age.

METHODS

Data Source and Population

The evaluation was conducted using the Surveillance Epidemiology, End Results (SEER)- and Medicare-linked database. SEER is a population-based cancer registry linked to Medicare administrative claims data. The areas represented in the SEER database are Atlanta, Georgia; Connecticut; Detroit, Michigan; greater California; greater Georgia; Hawaii; Iowa; Kentucky; Los Angeles, California; Louisiana; New Jersey; New Mexico; rural Georgia; San Francisco, California; San Jose, California; Seattle, Washington; and Utah. The data include cancer patient information on tumor site, stage at diagnosis, tumor characteristics, patient demographics and socioeconomic status, and healthcare services (utilization and costs).[29] Validity of the data to assess healthcare service utilization, especially chemotherapy, was established by previous studies.[30,31]

For the completeness of claims data, patients with Medicare Parts A and B enrollment (from diagnosis to death/end of study) without any health maintenance organization (HMO) enrollment were included. Patients aged 65 to 94 years who were diagnosed with primary NSCLC, at American Joint Committee on Cancer stage IIIB/IV, between January 2006 and December 2009, were included in the study (n = 30,077). Data prior to 2006 were excluded because bevacizumab was approved for patients with NSCLC in 2006. Patients were excluded if the cancer diagnosis was based on autopsy or death certificate, as the outcome had occurred and exposure could not be measured (n = 33). Patients with NSCLC who died within 30 days of diagnosis were excluded due to insufficient follow-up time to measure treatment (n = 5647). Additionally, 105 patients were excluded because their race and socioeconomic status were unknown, leaving 24,292 eligible for the study.

Treatment Groups

Patients were categorized into treatment groups based on the chemotherapy or targeted therapy received during the first 4 months after diagnosis.[32] Patients without any claims for chemotherapy/targeted therapy were grouped as "no chemotherapy." Those with claims for only platinum drugs (ie, carboplatin, cisplatin, and oxaliplatin) were grouped as "platinum-based chemotherapy." Those with claims for both platinum drugs and targeted therapy (ie, bevacizumab, cetuximab, and panitumumab) were grouped as "platinum + targeted therapy."

Of the 24,292 eligible patients, 22,117 NSCLC patients (grouped as no chemotherapy: 13,067; platinum-based chemotherapy: 7412; platinum + targeted therapy: 1638) were considered for the analysis and 2175 patients who received other chemotherapy were excluded from the primary analysis due to heterogeneity of treatments. To account for the selection bias due to observable factors, a 1:1:1 propensity score matching was conducted using the nearest-neighbor method.[33] The propensity score was derived from a multinomial logistic regression with age, gender, race, socioeconomic status, marital status, tumor stage, comorbidity score, tumor grade, tumor size, receipt of surgery, region, and year of diagnosis as independent variables.

Effectiveness of Chemotherapy

Effectiveness measures, life-years gained and quality-adjusted life-years (QALYs) gained were calculated using overall survival by the end-of-study follow-up (December 31, 2010). Health state utilities were extracted from the literature (see **Table 1**)[20,24,34,35]; the utility values were disease-phase–specific and were adjusted for minor and major treatment toxicity within the initial phase of treatment and for recurrence in the continuing phase of treatment. Each patient's overall survival was divided into initial, continuing, and terminal phases. The first 6 months after diagnosis were considered the initial phase, the last 3 months of life were designated the terminal phase, and the time between the initial phase and terminal phase was defined as the continuing phase. Overall survival time for patients living less than 3 months was allocated to the terminal phase in its entirety. Patients living more than 3 but less than 10 months had their last 3

Table 1. Published Utility Weights Assigned to Various Disease Phases in Base-Case and Alternative Scenarios[20,24,34,35]

Treatment Phases	Base-Case Scenario	Best-Case Scenario	Worst-Case Scenario
Initial Phase (6 months)			
No chemotherapy	0.63		
Adjuvant chemotherapy: no or moderate toxicity	0.58	0.71	0.46
Adjuvant chemotherapy: severe toxicity	0.46		
Continuing Phase	0.75	0.85	0.68
Recurrence	0.47	0.58	0.3
Terminal Phase (last 3 months of life)	0.25	0.35	0.18

months of life allocated to the terminal phase, with the remaining time allocated to the initial phase. Patients alive at the end of study had their survival time allocated to the initial phase and continuing phase.

During the initial phase, the presence/absence of adverse events (AEs) was assessed and health state utility values were assigned accordingly (Table 1). Defined AEs included anemia, hemolytic anemia, diarrhea, nausea, vomiting, neutropenia, stomatitis, and thrombocytopenia.[36] AEs were classified as moderate if reported in outpatient claims and severe if reported in inpatient claims. Within the continuing phase, patients were considered to have relapsed if a chemotherapy/targeted therapy was administered after a gap of at least 4 months (± 15 days) and the associated relapse utility was assigned to the remaining continuing phase.[37] Life-years were calculated by summing the time spent in each phase, and QALYs were calculated by multiplying the health state utilities with time in each phase and summing all phase-specific QALYs. Mean life-years and QALYs were estimated and discounted at a 3% annual rate for each treatment group using a Kaplan-Meier analysis.

Cost Analysis

A payer perspective was adopted, with cost based on Medicare amount paid for healthcare services. Total healthcare costs, which include inpatient services, outpatient services, provider services, skilled nursing facility, hospice, and durable medical equipment, were measured for each patient from diagnosis until death or end of study and by disease phase. Costs were adjusted for geographic location and inflation using county-level price adjusters because the study included patients across 16 US regions with cost information over 5 years.[38] Price adjusters were matched with the patient's county at diagnosis, allowing for cost adjustment to 2009 US$. Further inflation adjustment to 2014 US$ was based on the medical care component of the Consumer Price Index and a 3% annual discounting was applied to total healthcare costs.[39]

Cost-Utility Analysis

Cost-effectiveness was evaluated using the incremental cost-effectiveness ratio (ICER) and the net monetary benefit (NMB) method. ICERs were computed as the ratio of difference in mean total healthcare costs divided by the difference in mean life-years and QALYs.[40] The NMB approach incorporates changes in costs and effectiveness into a linear regression.[40-42] NMB is defined as λb_{ij}-c_{ij}, where λ is the willingness-to-pay per QALY threshold, b_{ij} is the effectiveness, and c_{ij} is the cost of treatment j for patient i.[42] Two NMB regression analyses were conducted: the first compared platinum-based chemotherapy with no chemotherapy and the second compared platinum + targeted therapy with platinum-based chemotherapy. The threshold value varied from $5000 to $400,000 for platinum-based chemotherapy versus no chemotherapy and from $50,000 to $1,000,000 for platinum + targeted therapy versus only platinum-based chemotherapy.

The results were presented as cost-effectiveness acceptability curves (CEACs) and NMB values. Cost-effectiveness evaluation was conducted for all patients and for each age group (65-69, 70-74, 75-79, and 80-94 years). Sensitivity analysis was conducted for the best- and worst-case scenarios of utility assignment. Additionally, since a substantial number of patients were excluded due to propensity score matching, a secondary analysis was conducted with all patients using the inverse probability treatment weighting method and estimating the NMB value at $100,000 per QALY, $150,000 per QALY, and $200,000 per QALY.[43,44]

RESULTS

The final matched sample was composed of 4884 patients with advanced NSCLC, with 1628 in each of the treatment groups. Table 2 shows the characteristics among these 3 treatment groups. No statistically significant differences were observed after matching, and the treatment groups were similar across all measured characteristics (Table 2). A majority of patients were Caucasian, male, and married; nearly 80% had stage IV NSCLC at diagnosis, and about 60% had an unknown tumor grade. Few patients

Table 2. Distribution of Characteristics by Treatment Groups in Patients with Stage IIIB/IV NSCLC

	Column N (%)			
Characteristics	**No Chemotherapy**	**Platinum-Based Chemotherapy**	**Platinum + Targeted Therapy**	***P***
Total N = 4884	**N = 1628**	**N = 1628**	**N = 1628**	
Age, years				.933
65-69	571 (35.07)	551 (33.85)	554 (34.03)	
70-74	475 (29.18)	490 (30.1)	505 (31.02)	
75-79	400 (24.57)	397 (24.39)	391 (24.02)	
80-94	182 (11.18)	190 (11.67)	178 (10.93)	
Race/ethnicity				.306
Caucasian	1447 (88.88)	1460 (89.68)	1421 (87.29)	
African American	74 (4.55)	70 (4.3)	85 (5.22)	
Other	107 (6.57)	98 (6.02)	122 (7.49)	
Gender				.823
Male	876 (53.81)	889 (54.61)	872 (53.56)	
Female	752 (46.19)	739 (45.39)	756 (46.44)	
Marital status				.898
Married	1039 (63.82)	1037 (63.7)	1034 (63.51)	
Unmarried	43 (2.64)	48 (2.95)	53 (3.26)	
Unknown	546 (33.54)	543 (33.35)	541 (33.23)	
AJCC tumor stage				.151
Stage IIIB	317 (19.47)	331 (20.33)	361 (22.17)	
Stage IV	1311 (80.53)	1297 (79.67)	1267 (77.83)	
Tumor grade				.449
Poorly/undifferentiated	436 (26.78)	442 (27.15)	434 (26.66)	
Well/moderately differentiated	199 (12.22)	227 (13.94)	232 (14.25)	
Unknown	993 (61.00)	959 (58.91)	962 (59.09)	
Tumor size, cm				.798
<1.0	27 (1.66)	30 (1.84)	34 (2.09)	
1.0-<2.0	89 (5.47)	89 (5.47)	96 (5.9)	
2.0-<4.0	424 (26.04)	436 (26.78)	441 (27.09)	
≥4.0	615 (37.78)	575 (35.32)	565 (34.71)	
Unknown	473 (29.05)	498 (30.59)	492 (30.22)	
Surgery				.751
Yes	74 (4.55)	70 (4.3)	79 (4.85)	
No	1554 (95.45)	1558 (95.7)	1549 (95.15)	
Charlson comorbidity score				.794
0	677 (41.58)	665 (40.85)	674 (41.4)	
1	568 (34.89)	599 (36.79)	566 (34.77)	
2	238 (14.62)	230 (14.13)	232 (14.25)	
≥3	145 (8.91)	134 (8.23)	156 (9.58)	
SES (poverty level)				.910
1st (low SES)	284 (17.44)	289 (17.75)	290 (17.81)	
2nd	427 (26.23)	429 (26.35)	400 (24.57)	
3rd	405 (24.88)	412 (25.31)	425 (26.11)	
4th (high SES)	512 (31.45)	498 (30.59)	513 (31.51)	

(continued)

Table 2. Distribution of Characteristics by Treatment Groups in Patients with Stage IIIB/IV NSCLC *(continued)*

	Column N (%)			
Characteristics	**No Chemotherapy**	**Platinum-Based Chemotherapy**	**Platinum + Targeted Therapy**	***P***
Total N = 4884	**N = 1628**	**N = 1628**	**N = 1628**	
Year of diagnosis				.284
2006	307 (18.86)	329 (20.21)	306 (18.8)	
2007	431 (26.47)	448 (27.52)	431 (26.47)	
2008	432 (26.54)	372 (22.85)	427 (26.23)	
2009	458 (28.13)	479 (29.42)	464 (28.5)	
SEER area				.760
Midwest	176 (10.81)	177 (10.87)	202 (12.41)	
Northeast	305 (18.73)	304 (18.67)	289 (17.75)	
South	438 (26.9)	439 (26.97)	448 (27.52)	
West	709 (43.55)	708 (43.49)	689 (42.32)	

AJCC indicates American Joint Committee on Cancer; NSCLC, non-small cell lung cancer; SEER, Surveillance Epidemiology, End Results; SES, socioeconomic status.

received surgery (5%), and nearly 77% of patients had a comorbidity score of 0 or 1.

Total healthcare cost per month by disease phase and treatment group is shown in **eAppendix Table 1** (eAppendices available at **www.ajmc.com**). Platinum + targeted therapy had the highest per-month cost in the initial ($15,002) and continuing phases ($7159), while the no-chemotherapy group experienced the highest cost in the terminal phase ($14,026). In contrast, the platinum-based chemotherapy monthly cost was $12,841 in the initial phase, $4887 in the continuing phase, and $11,944 in the terminal phase. However, for patients surviving at least 6 months, the per-month terminal-phase cost was $6624 for no chemotherapy, $9700 for platinum-based chemotherapy, and $10,783 for platinum + targeted therapy.

Table 3 presents the effectiveness, total healthcare costs, and ICER by age and various chemotherapy groups. Among elderly patients of all age groups (65-94 years), platinum + targeted therapy was the most effective with 15.34 mean life-months and 9.44 mean quality-adjusted life-months (QALMs); this was followed by platinum-based chemotherapy (life-months: 14.44; QALMs: 8.89) and no chemotherapy (life-months: 8.03; QALMs: 4.79). Total healthcare cost was estimated to be $131,050 for platinum + targeted therapy, $91,435 for platinum-based chemotherapy, and $48,848 for no chemotherapy. The mean life-months and mean QALMs decreased for each treatment group with increase in age (Table 3). As expected, the longest mean life-months and QALMs were observed for patients aged 65 to 69 years and shortest for those aged 80 to 94 years (Table 3). Overall, the total health cost for treatment groups decreased with increasing age; for example, the average total healthcare cost for platinum-based chemotherapy was $97,494 for patients aged 65 to 69 years and $78,742 for those aged 80 to 94 years.

Table 3 also shows the ICERs per life-year gained (LYG) and ICER per QALY gained for all ages and by age groups. For elderly NSCLC patients, the ICER per LYG and ICER per QALY gained were $79,726 and $124,645, respectively, for platinum-based chemotherapy versus no chemotherapy. Comparing platinum + targeted therapy with platinum-based chemotherapy, the ICER per LYG was $528,200 and ICER per QALY gained was $864,327, respectively. Analyzing the results by age group, similar results emerged with ICERs for platinum-based chemotherapy versus no chemotherapy, ranging from $62,258 to $92,813 per LYG and $96,241 to $157,425 per QALY gained (Table 3), respectively. With the exception of the 75- to 79-year-old age group, where platinum + targeted therapy was dominated (it was more costly and less effective than platinum-based chemotherapy), the ICERs for platinum + targeted therapy versus platinum-based chemotherapy ranged from $371,594 to $761,680 per LYG and $748,818 to $1,667,314 per QALY gained, respectively (Table 3).

The CEAC (**Figure 1**) shows that platinum-based chemotherapy was nearly 100% cost-effective at the willingness-to-pay threshold of $200,000 per QALY, while platinum + targeted therapy was only 50% cost-effective at the threshold of $750,000 per QALY and about 70% cost-effective at the $1 million per QALY threshold. CEAC results were sensitive to age groups, with platinum-based chemotherapy (vs no chemotherapy) being cost-effective at relatively lower willingness-to-pay thresholds for the

Table 3. Effectiveness and Cost-Effectiveness for Treatment Groups

Treatment Groups	Effectiveness		Total Healthcare Cost ($)	ICER ($)	
	Mean Life-Months	Mean QALMs	Mean (SD)	Per Mean Life-Year Gained[a]	Per Mean QALY Gained[a]
All ages (65-94 years)					
No chemotherapy	8.03	4.79	48,848 (51,210)		
Platinum-based chemotherapy	14.44	8.89	91,435 (60,703)	79,726	124,645
Platinum + targeted therapy	15.34	9.44	131,050 (82,814)	528,200	864,327
65-69 years					
No chemotherapy	8.82	5.14	47,143 (52,104)		
Platinum-based chemotherapy	15.33	9.59	97,494 (62,385)	92,813	135,778
Platinum + targeted therapy	15.93	9.92	135,578 (85,311)	761,680	1,384,873
70-74 years					
No chemotherapy	8.16	4.89	54,164 (53,027)		
Platinum-based chemotherapy	13.65	7.93	94,045 (67,276)	87,172	157,425
Platinum + targeted therapy	14.98	8.59	135,230 (87,358)	371,594	748,818
75-79 years					
No chemotherapy	7.50	4.27	49,148 (53,733)		
Platinum-based chemotherapy	14.58	8.85	85,880 (53,812)	62,258	96,241
Platinum + targeted therapy	14.45	8.48	125,339 (77,044)	Dominated	Dominated
80-94 years					
No chemotherapy	6.28	3.33	39,668 (33,574)		
Platinum-based chemotherapy	13.09	7.68	78,742 (47,605)	68,853	107,790
Platinum + targeted therapy	13.91	7.96	117,646 (71,604)	569,327	1,667,314

ICER indicates incremental cost-effectiveness ratio; QALM, quality-adjusted life-month; QALY, quality-adjusted life-year.
[a]ICER per life-month gained and per QALM gained was calculated and multiplied by 12 to get ICER per life-year gained and per QALY gained.

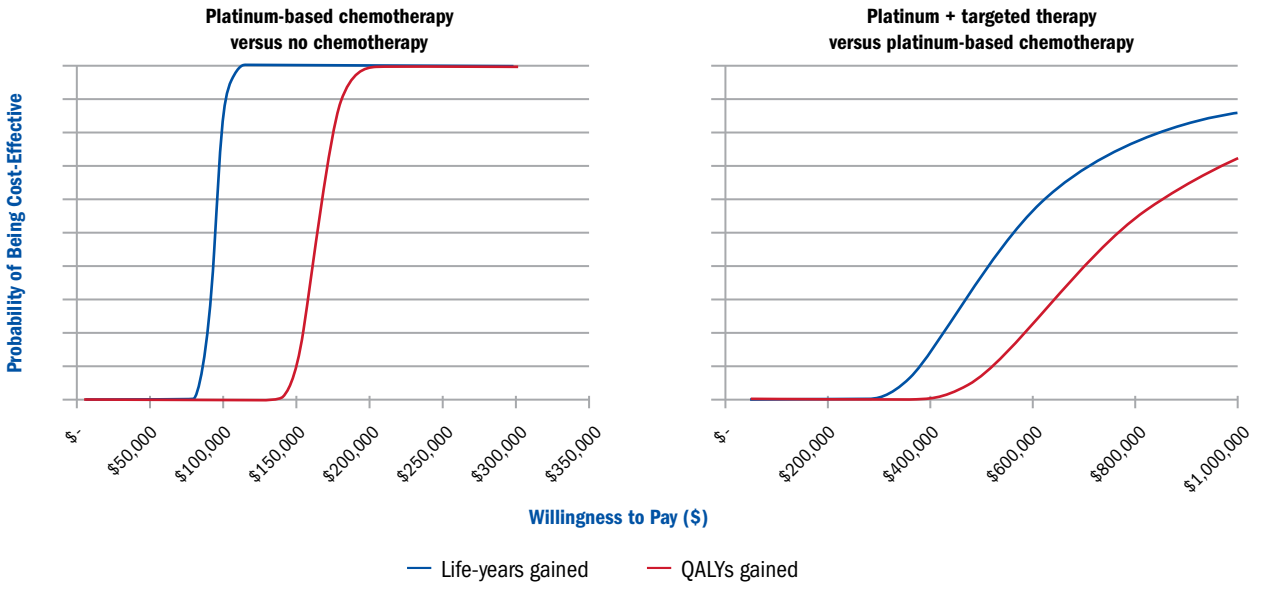
groups aged 75 to 79 years and 80 to 94 years compared with the groups aged 65 to 69 years and 70 to 74 years (**Figure 2**). Platinum + targeted therapy had a probability of being nearly 40% cost-effective at the willingness-to-pay threshold of $650,000 for the groups aged 65 to 69 years and 70 to 74 years; $1 million for the group aged 75 to 79 years; and $375,000 for the group aged 80 to 94 years. Additionally, the NMB values at a willingness-to-pay threshold of $100,000 per QALY, $150,000 per QALY, and $200,000 per QALY is shown in **eAppendix Table 2**. Results using the inverse probability treatment weight were similar to the base case results and are shown in **eAppendix Table 3**.

Similar to the base-case analysis, the ICER for platinum-based chemotherapy versus no chemotherapy was $101,197 per QALY gained and $143,552 per QALY for best- and worst-case scenarios, respectively; however, it was $709,522 per QALY and $834,000 per QALY for the best- and worst-case scenarios, respectively, when comparing platinum + targeted therapy with platinum-based chemotherapy (**eAppendix Table 4**). The best- and worst-case scenario results for ICER per QALY by age groups were similar to base-case results and are shown in eAppendix Table 4.

DISCUSSION

This study demonstrated that for all groups, combined, of patients 65 years or older, average cost, life-years, and QALYs increased as treatment regimens progressed from no chemotherapy to platinum-based chemotherapy to platinum + targeted therapy. Similar results hold for the analysis when stratified by age group, except for the group aged 75 to 79 years, which demonstrated a decline in life-years and QALYs for platinum + targeted therapy compared with platinum-based chemotherapy alone. The only regimen that falls within the commonly cited threshold of $100,000 per QALY is the platinum-based chemotherapy for the group aged 75 to 79 years. Even though older groups gained fewer years of life, the ICERs were lower for our oldest age groups compared with the younger groups. This may be the result of lower intensity of treatment compared with no chemotherapy, resulting in lower cost but no diminution of effect. While other comparisons of platinum-based chemotherapy with no chemotherapy were within about 150% of the commonly defined threshold, the ICER for the platinum + targeted therapy compared with platinum-based chemotherapy was 7 to 16

Figure 1. Cost-Effectiveness Acceptability Curves



QALY indicates quality-adjusted life-year.

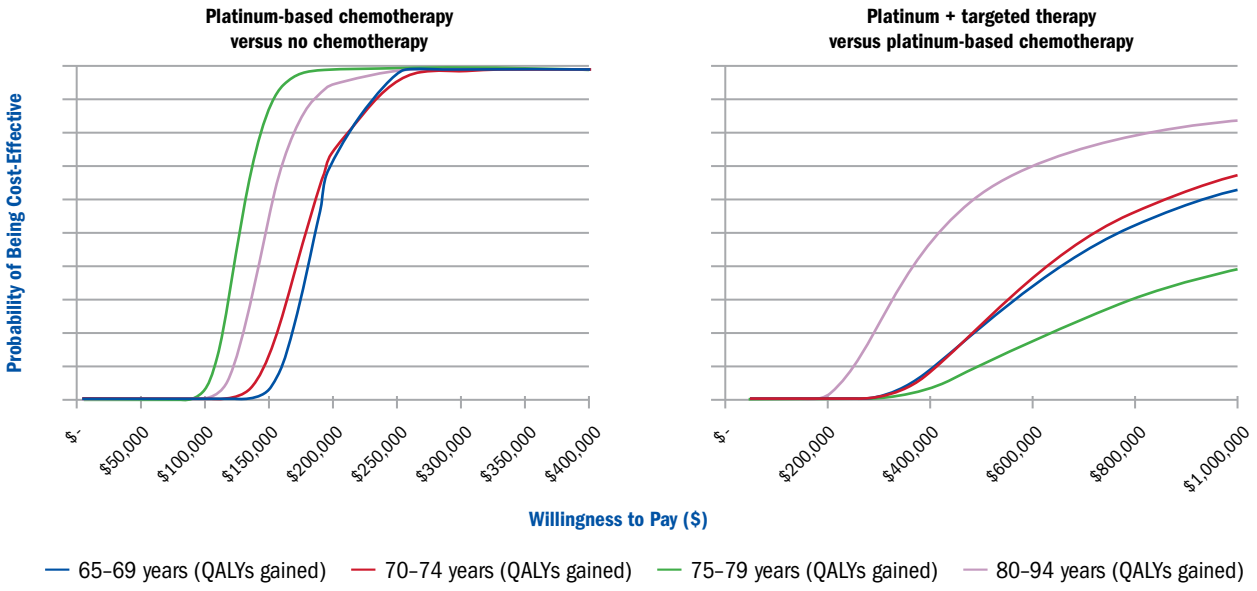
times the $100,000 willingness-to-pay per QALY threshold overall and within age groups.

Our results were consistent with 3 US studies that were based on decision analytic modeling with parameters based on clinical trials data, SEER-Medicare claims, and medical record data. Goulart et al reported the ICER per LYG and ICER per QALY for chemotherapy + bevacizumab compared with chemotherapy alone as $309,000 per LYG and $560,000 per QALY, respectively.[20] They also found that chemotherapy + bevacizumab was nearly 70% cost-effective at the willingness-to-pay threshold of $1 million. The study was based on a model that incorporated parameters from clinical trials, retrospective 1999-2003 SEER-Medicare claims data, and assumptions about drug utilization based on an average 63-year-old patient and several assumptions about healthcare utilization associated with AEs such as severe bleeding, febrile neutropenia episodes, and anemia.[20] The costs of lab tests and imaging were assumed to be the same per group and were excluded from the analysis.[20]

In contrast, our study was based on 2006 to 2009 comprehensive SEER-Medicare claims data inclusive of patients aged 65 to 94 years. Estimates from the literature were employed mainly to quantitate quality of life using health state utilities for various phases of illness and AEs identified in the data. Klein et al developed a Markov model populated with data from a randomized clinical trial, claims data, and Medicare drug costs.[24] The model was based on a number of assumptions, including that the probability of incurring AEs from treatment was not related to health state and patient response to treatment was not related to the occurrence of adverse effects. The model did not account for parameters related to dose reductions or delays between treatment cycles. They found the ICER per QALY of $1,006,065 when comparing targeted therapy-based regimens (carboplatin + paclitaxel + bevacizumab) with chemotherapy alone (cisplatin + pemetrexed). This study computed the average overall cost for all events and did not account for AEs.[24] As a result, the cost of treating serious side effects was the same for all regimens.[24]

In our study, side effects were identified from Medicare claims data and the information was analyzed to adjust for quality-of-life decrements associated with the AEs. Nonetheless, our results are comparable to those reported by Goulart et al and Klein et al, although the targeted therapies for our analysis also included cetuximab and panitumumab, which have been shown to be more expensive than bevacizumab.[20,24,45] Our platinum + targeted therapy group was nearly 73% cost-effective at a willingness-to-pay threshold of $1 million, which is very similar to the results estimated by Goulart et al.[20] A US study that utilized electronic medical record data and charges for outpatient care reported that platinum + targeted therapy, which is more costly and less effective, was dominated by nontargeted chemotherapy combinations.[22] Several other economic evaluations of alternative treatments for lung cancer have been published, but the results are not comparable to those

Figure 2. Cost-Effectiveness Acceptability Curves by Age Groups



QALY indicates quality-adjusted life-year.

of our study; those studies were conducted in European countries where the healthcare systems and cost structures differ greatly from those in the United States.[18,19,23,46]

Limitations

Our results should be interpreted in light of the limitations of the study. The study used claims data, and the treatments received by patients were not randomly assigned, thereby introducing the possibility of selection bias and confounding by indication. The use of 1:1:1 propensity score matching addressed bias due to selected measured factors, but dissimilarities between the groups due to unmeasured or unknown factors may affect patient outcomes. SEER–Medicare data do not include patients from all United States regions, so the study results may be generalizable only to participating regions. We excluded patients enrolled in managed care (HMOs) for the completeness of claims data, but treatment-related outcomes and payer costs may be similar for HMOs and other fee-for-service payment models.[47] The payer perspective excluded indirect costs, such as lost wages due to decreased work productivity, but given the age of the population, indirect costs may be less important.

CONCLUSIONS

Overall, platinum-based chemotherapy and platinum + targeted therapy were effective in extending life-years and QALYs compared with no chemotherapy. There were reductions in the effectiveness of chemotherapy for NSCLC as patients became older. While the cost per QALY gained was within 150% of the commonly referenced US standard of $100,000 per QALY for platinum-based chemotherapy compared with no chemotherapy, the cost per QALY gained for platinum + targeted therapy was 7 to 16 times the $100,000 per LYG common standard.[48]

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eAppendix. Supplemental Tables

Table 1. Total Healthcare Costs in Different Disease Phases by Chemotherapy Type

Treatment groups	Total Healthcare Costs Per Month: Mean US$ (SD)
	Initial Phase[a] (6 months after diagnosis)
	N = 3839
No chemotherapy	13,434 (43,633)
Platinum-based chemotherapy	12,841 (30,081)
Platinum + targeted therapy	15,002 (18,575)
	Continuing Phase[a] (between initial and terminal phase)
	N = 2187
No chemotherapy	2967 (4029)
Platinum-based chemotherapy	4887 (5702)
Platinum + targeted therapy	7159 (5665)
	Terminal Phase[a] (3 months before death)
	N = 4228
No chemotherapy	14,026 (14,667)
Platinum-based chemotherapy	11,944 (9316)
Platinum + targeted therapy	13,544 (10,283)

[a]Costs incurred in the last 3 months of life were assigned to the terminal phase. If patients lived for less than or equal to 3 months, then all costs were assigned to the terminal phase. Similarly, costs incurred in the first 6 months following diagnosis were assigned to initial phase and if the patient lived more than 3 months but less than or equal to 9 months, then the costs remaining after 3 months of terminal phase were assigned to the initial phase. If the patient lived more than 9 months, then the time between the initial phase and terminal phase was assigned as continuing phase.

Table 2. Net Monetary Benefit by Treatment Groups and Age Groups

	Net Monetary Benefit at WTP $100,000/QALY ($)		**Net Monetary Benefit at WTP $150,000/QALY ($)**		**Net Monetary Benefit at WTP $200,000/QALY ($)**	
	Platinum-based chemotherapy versus No chemotherapy	Platinum + Targeted therapy versus Platinum-based chemotherapy	Platinum-based chemotherapy versus No chemotherapy	Platinum + Targeted therapy versus Platinum-based chemotherapy	Platinum-based chemotherapy versus No chemotherapy	Platinum + Targeted therapy versus Platinum-based chemotherapy
All ages	–16,551	–34,449	–3533	–31,866	9485	–29,283
6569 years	–23,208	–33,130	–9636	–30,652	3935	–28,175
70-74 years	–17,512	–35,484	–6327	–32,634	4858	–29,784
75-79 years	–7794	–36,664	6675	–35,267	21,144	–33,870
80-94 years	–12,454	–29,639	856	–25,007	14,167	–20,375

QALY indicates quality-adjusted life-year; WTP, willingness to pay.

Table 3. Net Monetary Benefit Using Inverse Probability Treatment Weighting

Net Monetary Benefit	Platinum-Based Chemotherapy vs No Chemotherapy	Platinum + Targeted Therapy vs Platinum-Based Chemotherapy
WTP $100,000/QALY ($)	–17,013	–33,188
WTP $150,000/QALY ($)	–5489	–31,835
WTP $200,000/QALY ($)	6037	–30,481

QALY indicates quality-adjusted life-year; WTP, willingness to pay.

Table 4. Effectiveness and Cost-Effectiveness for Chemotherapy Treatment Groups

	Mean QALM		Total Healthcare Cost ($)	ICER ($) Per Mean QALY Gained[a]	
	Best-Case Scenario	Worst-Case Scenario	Mean (SD)	Best-Case Scenario	Worst-Case Scenario
All ages (65-94 years)					
No chemotherapy	5.56	4.02	48,848 (51,210)		
Platinum-based chemotherapy	10.61	7.58	91,435 (60,703)	101,197	143,552
Platinum + targeted therapy	11.28	8.15	131,050 (82,814)	709,522	834,000
65-69 years					
No chemotherapy	5.97	4.25	47,143 (52,104)		
Platinum-based chemotherapy	11.43	8.19	97,494 (62,385)	110,662	153,353
Platinum + targeted therapy	11.83	8.57	135,578 (85,311)	1,142,520	1,202,653
70-74 years					
No chemotherapy	5.67	4.11	54,164 (53,027)		
Platinum-based chemotherapy	9.58	6.82	94,045 (67,276)	122,397	176,595
Platinum + targeted therapy	10.39	7.28	135,230 (87,358)	610,148	1,074,391
75-79 years					
No chemotherapy	4.97	3.54	49,148 (53,733)		
Platinum-based chemotherapy	10.53	7.61	85,880 (53,812)	79,278	108,301
Platinum + targeted therapy	10.19	7.32	125,339 (77,044)	Dominated	Dominated
80-94 years					
No chemotherapy	3.92	2.69	39,668 (33,574)		
Platinum-based chemotherapy	9.24	6.41	78,742 (47,605)	88,137	126,045
Platinum + targeted therapy	9.56	6.81	117,646 (71,604)	1,458,900	1,167,120

ICER indicates incremental cost-effectiveness ratio; QALM, quality-adjusted life-month; QALY, quality-adjusted life-year.
[a]ICERs per life-month gained and per QALM gained were calculated and multiplied by 12 to get ICER per life-year gained and per QALY gained.