Second-line and Third-line Chemotherapy for Lung Cancer: Use and Cost

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Lung cancer is the second most common cancer in the United States and is the most common cause of cancer-related death. The American Cancer Society[1] estimated that there would be 213,380 new cases of lung cancer diagnosed in the United States and 160,390 deaths from this disease in 2007. Most of these individuals have regional or advanced disease at diagnosis and are eligible for chemotherapy. Many who begin chemotherapy show signs of disease progression or must discontinue first-line therapy because of intolerable adverse effects and are eligible for subsequent chemotherapy with different agents. Second-line chemotherapy can produce symptomatic improvement, objective responses, and modest improvements in survival for patients with advanced disease.[2-5] Despite the availability of second- and third-line therapies, there is disagreement about the best treatment strategy.[6] Little is known regarding patterns of chemotherapy use and cost of care for persons who receive such treatment.

Using data from a large nationwide health insurer, we sought to determine the most common forms of second- and third-line chemotherapy use for persons with lung cancer. We also evaluated key services utilization (hospital days, ambulatory visits, and emergency department visits), and lifetime costs of care following initiation of the second-line chemotherapy regimen to determine if 1 or more regimens had a significant effect on costs of care relative to others (data not shown).

METHODS

Database and Patient Population

We identified patients with lung cancer from a health insurance database (i3, Ingenix, UnitedHealthcare) representing privately insured patients and individuals enrolled in Medicare + Choice and Medicaid across all 50 states, the District of Columbia, and the US Virgin Islands.[7] We searched administrative records for patients diagnosed as having lung cancer between January 1, 2002, and December 31, 2006, who had received at least 1 chemotherapy agent since diagnosis, using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for malignant neoplasm of trachea, bronchus, and lung; malignant neoplasm of pleura; or carcinoma in situ of respiratory system (codes 162.xx, 163.xx, and 231.xx). To eliminate "false positives," patients with ICD-9-CM lung cancer codes for whom lung cancer was being ruled out or patients being treated for other

Objectives: To identify commonly prescribed first-, second-, and third-line chemotherapy regimens for persons with lung cancer and to evaluate the utilization patterns and costs of care associated with receiving these regimens.

Study Design: Retrospective data analysis.

Methods: Using health insurance claims from January 1, 2002, through December 31, 2006, patients with lung cancer were identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes. An algorithm was developed to identify first-, second-, and third-line chemotherapy. Patients were stratified by the number of discrete regimens received or by their specific chemotherapy agent or combination of agents. Data were analyzed for up to 2 years from the date of the initial first-line regimen and for 1 year from the second and third lines. Patient costs were based on total reimbursements for each group during the observation period.

Results: Of patients receiving first-line chemotherapy, 25% and 10% received second-line and third-line chemotherapy, respectively. Docetaxel, gefitinib, and erlotinib hydrochloride were the most commonly prescribed second-line regimens; gefitinib and docetaxel were the most commonly prescribed third-line regimens. The most commonly prescribed second- and third-line agents changed substantially over time. Total costs and costs per patient per month increased as the number of lines of chemotherapy prescribed increased.
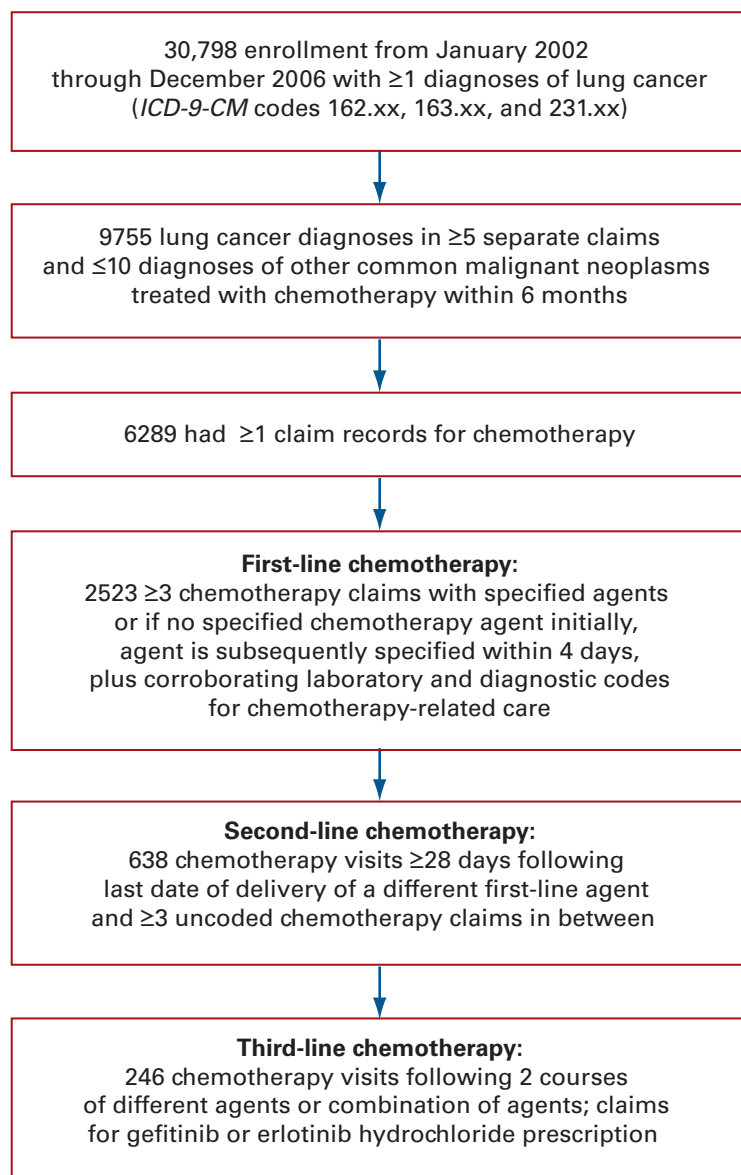
Conclusions: Second- and third-line chemotherapy is prescribed infrequently, and patterns of prescribing are changing over time. Direct medical care costs increase substantially with additional lines of therapy.

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■ **Figure 1.** Algorithm for Identifying Patients With Lung Cancer Having Multiple Lines of Chemotherapy

ICD-9-CM indicates *International Classification of Diseases, Ninth Revision, Clinical Modification.*

level II procedure and diagnosis codes were utilized to identify chemotherapy administration cycles. Selecting cases for analysis proved to be problematic due to variation in coding methods among service providers, most notably relating to the common use of *ICD-9-CM* diagnosis code V58.1 (encounter for antineoplastic chemotherapy and immunotherapy), which has been previously noted to be an unreliable indicator of chemotherapy administration.[8,9] Initially, patients were excluded if they had only chemotherapy administration codes for a date of service with no agent specified. However, we found many cases in which dates of service with *ICD-9-CM* code V58.1 and HCPCS agent codes were closely followed by dates of service for which V58.1 was the only code denoting the visit as a chemotherapy encounter. Often this pattern was repeated several times. Closer examination of the service dates without an agent often revealed laboratory, diagnostic, and palliative procedures related to chemotherapy management. Based on this observation, we surmised that providers used *ICD-9-CM* code V58.1 for chemotherapy-related services and for chemotherapy administration.

We allowed patients in our analysis set to have up to 4 consecutive dates of service at the beginning of their regimen in which *ICD-9-CM* code V58.1 was used to indicate a chemotherapy encounter but no specific agents were recorded, provided that afterward at least 3 service dates were coded with specific agents. Subsequently, patients with more than 8 consecutive nonspecific chemotherapy encounters were excluded from the analysis. Common first-line agent combinations were based on those listed in the National Cancer Institute's Physician Data Query (PDQ) database.[10,11]

cancers, we required claims records with *ICD-9-CM* lung cancer codes on at least 5 separate dates of service and no more than 10 dates of service with diagnoses of other common malignant neoplasms that are treated with chemotherapy recorded between 30 days before and 6 months after the initial lung cancer diagnosis (**Figure 1**).

First-line Chemotherapy Use

The *ICD-9-CM, Current Procedural Terminology 4*, and Healthcare Common Procedure Coding System (HCPCS)

Second-line and Third-line Chemotherapy

Second-line therapy is administered for disease progression, recurrence, or intolerable adverse effects following administration of initial chemotherapy. We defined a second-line chemotherapy agent in 1 of 2 ways. First, a second-line agent

could be injectable; if so, then the agent was one with an initial injectable administration date that was at least 28 days following the last delivery date of a different first-line chemotherapy agent or widely recognized combination of agents. Second, oral agents such as erlotinib hydrochloride and gefitinib, which are used after failure of first-line chemotherapy, were counted as second-line agents if the initial date on which the prescription was filled occurred on or after the last date of administration of first-line chemotherapy.

For inclusion, second-line regimens had to meet the same criteria as the first line, as well as having no more than 3 uncoded chemotherapy visits between the last recorded date of the first-line treatment and the initiation of the second. If the patient received chemotherapy beyond his or her first-line treatment and the pattern of second-line administration did not meet the criteria, the patient was excluded from the analysis. We looked specifically for US Food and Drug Administration (FDA)-approved second-line therapies, including docetaxel, pemetrexed disodium, erlotinib, and gefitinib.

We defined third-line chemotherapy as any third chemotherapy agent with an initial administration date following 2 separate courses of treatment. Because of heterogeneity in prescribing and difficulty in identifying regimens as defined by the PDQ or as labeled by the FDA, agents identified as third-line therapy represent only the first drug given in the third-line setting.

Evaluating Resource Use and Cost of Care

Resource utilization was based on claims. Costs were based on health plan reimbursements for all goods and services covered by the plan. Key services were grouped into inpatient days, outpatient visits, chemotherapy, emergency department visits, laboratory, outpatient pharmacy, and skilled nursing facility, hospice, or home care days. The costs of chemotherapy represent injectable chemotherapy agents; the costs of agent administration and related procedures are accounted for in other categories. Oral oncologic agents are captured under outpatient pharmacy. Laboratory costs include the actual processing of the specimen. Using the Kaplan-Meier sample average (KMSA) estimator method, we estimated 1-year and 2-year total costs for patients with lung cancer.[12] The KMSA estimator of the total cost of care is given by the following equation: $E = \Sigma_i P_i * E_i$, where i denotes month from diagnosis (0 denotes the diagnosis month); P_i, the probability of being observed in month i; and E_i, the mean cost incurred in month i among all cases observed to this time. E_i includes the costs of cases surviving through month i and of cases dying in month i. Total expected costs and variances around expected costs are included, using an expression for variance that was developed for the KMSA estimator.[13] In accordance with standards for economic evaluation, results for all cost estimates are presented with costs in future years discounted at annual rates of 3%.[14]

Utilization and the aforementioned key services costs are reported for lung cancer cases from the date of initial chemotherapy administration of the patient's first-, second-, or third-line regimen. Data were analyzed for the first and second years from the date of a patient's first-line therapy and were further stratified by whether he or she had only first-line therapy, first- and second-line therapy, or therapy beyond a second-line regimen. Analysis beginning with the initiation of second- and third-line chemotherapy regimens had only a 1-year time horizon. To determine how the choice of initial therapy affects cost of care, subjects were stratified by initial type of therapy.

Because the marketing of gefitinib was restricted midway through our analysis period, we only include persons receiving this medication in the summary statistics. We exclude gefitinib recipients from the logistic regression and utilization analyses.

RESULTS

The initial search yielded 30,798 individuals older than 20 years with at least 1 diagnosis code for lung cancer enrolled between January 1, 2002, and December 31, 2006. Applying exclusion criteria ruled out diagnoses of other cancers and reduced the sample to 11,953 patients; of those, 6289 had at least 1 claim record indicating that they had received chemotherapy. After applying restrictions for having a minimum number of agents specified along with an administration code as already outlined, 2523 patients were included in the analysis. Eighty-one percent of these individuals were covered by commercial insurance, 17% through Medicare contracts, and 2% through Medicaid contracts.

The mean interval between the last date of administration of the first-line agent and the initiation of the second-line treatment was 114 days for injectable agents. Almost half (46%) of the patients received second-line therapy within 60 days of the last date of administration of first-line therapy. An additional 24% received second-line therapy within 120 days of first-line therapy. Among the remaining 30%, the period between first and second treatments ranged from 121 to 844 days.

Among patients who had second-line therapy, patients receiving docetaxel had recorded claims for the greatest number of months (mean, 8.8 months) after the initiation of therapy, while those receiving erlotinib had the fewest num-

■ **Table 1.** Second-line Agents and Agent Combinations Other Than Single-Agent Second-line Therapy With Docetaxel, Pemetrexed Disodium, or Erlotinib Hydrochloride

Variable	No. of Patients
Gefitinib	70
Topotecan	52
Gemcitabine hydrochloride	33
Carboplatin + paclitaxel	30
Carboplatin + gemcitabine	26
Cisplatin + irinotecan	23
Carboplatin + docetaxel	21
Gemcitabine + vinorelbine	20
Paclitaxel	17
Vinorelbine	14
Cisplatin + gemcitabine	13
Docetaxel + gemcitabine	13
Carboplatin + etoposide phosphate	12
Cisplatin + docetaxel	11
Cisplatin + etoposide	10
Carboplatin + irinotecan	6
Docetaxel + pemetrexed disodium	5
Cisplatin	3
Gemcitabine + pemetrexed	3
Gemcitabine + irinotecan	2
Carboplatin + vinorelbine	1
Total	**385**

ber of claims months (mean, 5.4 months). Because erlotinib did not become available until December 2004, a higher relative percentage of patients began therapy toward the end of the observation period, resulting in a shorter observation time. For second-line therapy, an additional 385 agents or chemotherapy combinations were observed in the data; the most common regimens are given in **Table 1**.

Chemotherapy Prescribing Patterns

Of 2523 persons included in the analysis, the most commonly prescribed first-line regimen was carboplatin and paclitaxel. Carboplatin in combination with etoposide phosphate, gemcitabine hydrochloride, and docetaxel was also commonly prescribed (**Table 2**).

Of patients receiving first-line chemotherapy, 25% received second-line therapy. Docetaxel was the most common second-line agent, but there was much more variation for second-line chemotherapy agents and combinations than for first-line treatments. Gefitinib was the second most commonly prescribed second-line agent, but the use of gefitinib as a proportion of all

second-line therapies declined rapidly during the period of observation after findings from clinical studies suggested that it did not improve survival and after the subsequent FDA labeling change. In contrast, erlotinib prescriptions increased substantially between 2004 (the year of its FDA approval) and 2005 (**Figure 2**).

Only 10% of first-line patients received third-line chemotherapy. Gefitinib was most commonly prescribed overall, but over time erlotinib replaced gefitinib as the most commonly prescribed third-line agent after the labeling of gefitinib was modified in June of 2005 to severely reduce its access (Figure 2).

The logistic regression analysis showed that age, choice of first-line regimen, time to initial treatment, and diagnosis year were significantly associated with receiving second-line treatment. Older persons were significantly less likely to receive second-line chemotherapy, but the odds ratio (OR) was only marginally different from 1 (OR, 0.97; 95% confidence interval [CI], 0.96-0.98). Likewise, increasing time from initial diagnosis to treatment was associated with lower likelihood of receiving second-line therapy (OR, 0.83; 95% CI, 0.75-0.92). Using cisplatin plus etoposide as the reference regimen, we found that persons receiving carboplatin plus etoposide (OR, 0.56; 95% CI, 0.39-0.79) and carboplatin plus paclitaxel (OR, 0.73; 95% CI, 0.55-0.97) were significantly less likely to receive second-line chemotherapy. No other major first-line chemotherapy regimen was significantly associated with the likelihood of receiving second-line chemotherapy.

Utilization and Cost for Those Receiving Second-line and Third-line Chemotherapy

We compared overall costs for persons receiving only first-line chemotherapy vs additional chemotherapy regimens. Patients receiving first-line therapy only were observed for a mean of 8.1 months vs 11.8 months among those receiving first- vs second-line therapy and for a mean of 16 months among persons receiving third-line therapy. In the first 12 months following the administration of chemotherapy, the costs per patient per month (PPPM) were similar for the different regimens among persons receiving only first-line therapy (**Table 3**), ranging from approximately $3500 to $3900. The PPPM costs in the first 12 months for those receiving first- and second-line therapy were highest for those receiving carboplatin plus docetaxel as first-line therapy and were lowest for those receiving carboplatin plus etoposide. The PPPM

■ **Table 2.** Number of Patients and Number of Months Observed by Common First-line, Second-line, and Third-line Therapies

Variable	No. of Patients	No. of Months Observed, Mean		No. of Patients	No. of Months Observed, Mean		No. of Patients	No. of Months Observed, Mean
Patients Who Received First-line Therapy			**Patients Who Received Second-line Therapy (Single-agent Administration Only)**			**Patients Who Received Third-line Therapy**		
Carboplatin + paclitaxel	1335	7.62	Docetaxel	149	8.57	Docetaxel	32	5.53
Carboplatin + etoposide phosphate	439	6.99	Pemetrexed disodium	31	6.42	Pemetrexed	28	5.35
Cisplatin + etoposide	306	7.16	Erlotinib hydrochloride	73	5.44	Erlotinib	31	5.30
Carboplatin + docetaxel	234	7.00	Other agent	385	7.04	Other agent	155	4.87
Carboplatin + gemcitabine hydrochloride	209	7.05						
Total	**2523**	7.35	Total	**638**	7.19	Total	**246**	5.07
Patients Who Received First-line Therapy Only			**Patients Who Received First- and Second-line Therapy Only**			**Patients Who Received Chemotherapy Beyond the Second Line of Therapy**		
Carboplatin + paclitaxel	995	8.67	Carboplatin + paclitaxel	208	12.37	Carboplatin + paclitaxel	132	16.40
Carboplatin + etoposide	350	7.49	Carboplatin + etoposide	62	11.74	Carboplatin + etoposide	39	14.95
Cisplatin + etoposide	208	7.49	Cisplatin + etoposide	89	11.89	Cisplatin + etoposide	36	16.22
Carboplatin + docetaxel	177	7.64	Carboplatin + docetaxel	33	9.51	Carboplatin + docetaxel	24	15.50
Carboplatin + gemcitabine	155	7.64	Carboplatin + gemcitabine	39	10.92	Carboplatin + gemcitabine	15	15.87
Total	**1885**	8.06	Total	**431**	11.81	Total	**246**	16.02

costs were incrementally higher for those who received third-line vs second-line vs first-line chemotherapy regardless of initial first-line regimen, with PPPM costs ranging from $7200 to $9600 for those receiving 3 lines of chemotherapy.

Far fewer individuals were observed in the second 12 months from the date of initial chemotherapy administration, reflecting poor survival for persons with lung cancer (Table 3). For those who were observed in the second 12 months, the total and PPPM costs were incrementally higher for those receiving second- and third-line treatments.

Starting from the point of initial second-line treatment, PPPM reimbursements were highest for persons receiving pemetrexed as second-line therapy and

■ **Figure 2.** Gefitinib and Erlotinib Hydrochloride Prescriptions Filled per Month Between May 2003 and September 2005[a]
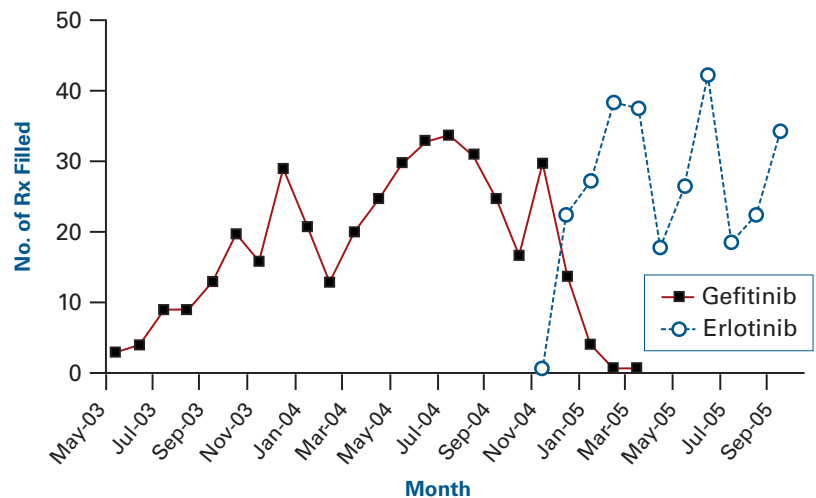
[a]Includes all prescriptions for erlotinib and gefitinib among the study group.

■ **Table 3.** Patient Costs by First-line Therapy

Variable	No. of Patients	Cost, Mean (SE), $		
		Chemotherapy Administration[a]	Emergency Department	Inpatient
For Months 1 Through 12 Following Initiation of Chemotherapy (n = 2523)				
Patients who received first-line therapy only				
Caroplatin + paclitaxel	995	10,696 (272)	925 (84)	10,576 (1290)
Carboplatin + etoposide phosphate	350	6819 (302)	983 (142)	6641 (920)
Cisplatin + etoposide	208	2970 (193)	709 (165)	10,116 (1619)
Carboplatin + docetaxel	177	12,154 (686)	2326 (967)	9138 (2595)
Carboplatin + gemcitabine hydrochloride	155	12,343 (775)	1243 (372)	7957 (1381)
Patients who received first- and second-line therapy only				
Carboplatin + paclitaxel	208	20,444 (773)	2377 (609)	19,592 (2752)
Carboplatin + etoposide	62	12,895 (1023)	3237 (1309)	9682 (2119)
Cisplatin + etoposide	89	11,895 (701)	2579 (709)	16,890 (4252)
Carboplatin + docetaxel	33	23,056 (2090)	1275 (593)	18,012 (3035)
Carboplatin + gemcitabine	39	20,801 (1883)	1443 (545)	13,900 (4160)
Patients who received chemotherapy beyond the second line of therapy				
Carboplatin + paclitaxel	132	27,658 (1473)	1399 (320)	8945 (1418)
Carboplatin + etoposide	39	22,068 (1772)	1000 (316)	16,394 (5595)
Cisplatin + etoposide	36	16,209 (2151)	2689 (1238)	16,110 (5311)
Carboplatin + docetaxel	24	32,206 (2779)	3206 (1709)	19,668 (6386)
Carboplatin + gemcitabine	15	23,459 (2453)	1629 (898)	17,207 (8131)
For Months 12 Through 24 Following Initiation of Chemotherapy (n = 779)				
Patients who received first-line therapy only				
Carboplatin + paclitaxel	269	193 (108)	585 (219)	3963 (827)
Carboplatin + etoposide	69	332 (137)	828 (289)	4837 (1299)
Cisplatin + etoposide	41	384 (457)	330 (231)	5216 (2596)
Carboplatin + docetaxel	37	0	673 (382)	9282 (3426)
Carboplatin + gemcitabine	32	340 (364)	516 (387)	8759 (4282)
Patients who received first- and second-line therapy only				
Carboplatin + paclitaxel	90	4444 (1032)	728 (277)	7063 (2065)
Carboplatin + etoposide	18	4217 (1308)	447 (295)	2664 (1313)
Cisplatin + etoposide	27	1960 (1202)	2447 (1414)	17,677 (9140)
Carboplatin + docetaxel	9	4514 (2728)	129 (86)	6557 (5767)
Carboplatin + gemcitabine	13	4637 (2373)	2017 (1922)	16,648 (13,793)
Patients who received chemotherapy beyond the second line of therapy				
Carboplatin + paclitaxel	95	12,214 (1620)	1237 (372)	11,181 (2338)
Carboplatin + etoposide	27	6824 (1662)	567 (213)	11,010 (5267)
Cisplatin + etoposide	30	7597 (2144)	2271 (1121)	9567 (3062)
Carboplatin + docetaxel	14	13,433 (4613)	1549 (772)	2364 (1340)
Carboplatin + gemcitabine	8	13,117 (5372)	0	18,643 (19,145)
Carboplatin + gemcitabine	8	13,117 (5372)	0	18,643 (19,145)

[a]Includes injectable chemotherapy only.

		Cost, Mean (SE), $			
Laboratory	**Outpatient**	**Outpatient Rx**	**Skilled Nursing Facility**	**Total**	**Per Patient Per Month**
547 (28)	19,592 (669)	1863 (93)	553 (52)	**44,750** (1635)	3729
530 (48)	27,819 (1283)	1897 (132)	819 (178)	**45,508** (1953)	3792
562 (60)	26,359 (1331)	2072 (187)	588 (124)	**43,376** (2366)	3615
450 (50)	20,555 (1399)	2073 (298)	974 (343)	**47,670** (4512)	3972
559 (77)	18,246 (1311)	2084 (257)	505 (121)	**42,937** (2802)	3578
1033 (87)	35,603 (1796)	3556 (321)	1020 (228)	**83,625** (4211)	6969
749 (149)	39,432 (4288)	3276 (490)	1108 (378)	**70,379** (6460)	5865
1168 (188)	46,650 (2734)	3917 (474)	994 (618)	**84,093** (6037)	7008
887 (158)	36,143 (4839)	4007 (692)	2534 (771)	**85,914** (8133)	7159
1121 (186)	31,496 (4492)	4083 (825)	638 (185)	**73,482** (8529)	6124
967 (102)	41,093 (2751)	5543 (1,405)	745 (198)	**86,350** (4577)	7196
1190 (224)	56,429 (5968)	5785 (1,510)	817 (255)	**103,683** (10,856)	8640
1080 (132)	55,327 (4688)	3902 (683)	625 (267)	**95,942** (9306)	7995
685 (105)	55,357 (10,759)	3507 (730)	986 (381)	**115,615** (14,135)	9635
1268 (316)	40,947 (7038)	4216 (996)	1801 (1425)	**90,527** (16,202)	7544
275 (31)	6326 (855)	1307 (143)	354 (94)	**13,003** (1557)	1084
212 (47)	5993 (960)	1407 (207)	724 (278)	**14,333** (2154)	1195
238 (76)	5295 (1625)	1107 (269)	1742 (1339)	**14,312** (4042)	1193
281 (90)	5787 (1547)	2083 (531)	1808 (1360)	**19,914** (4486)	1659
385 (152)	7805 (2396)	1455 (385)	469 (266)	**19,729** (5983)	1644
324 (60)	11,152 (1744)	2013 (411)	568 (165)	**26,292** (3749)	2191
275 (90)	10,461 (2832)	1136 (486)	822 (436)	**20,022** (3781)	1668
574 (175)	11,969 (2849)	2238 (514)	6578 (6167)	**43,443** (15,480)	3620
305 (188)	8707 (3535)	1163 (531)	0	**21,375** (10,923)	1781
164 (49)	6984 (3352)	993 (393)	662 (647)	**32,105** (20,122)	2675
606 (110)	18,133 (3010)	2598 (383)	875 (314)	**46,844** (5498)	3904
301 (76)	15,709 (2719)	3295 (1475)	408 (140)	**38,114** (6356)	3176
389 (93)	18,230 (4009)	1696 (343)	1169 (675)	**40,919** (7583)	3410
207 (76)	13,656 (5238)	2996 (1286)	990 (948)	**35,195** (10,628)	2933
690 (360)	13,422 (2586)	2033 (755)	1533 (1400)	**49,438** (21,479)	4120
690 (360)	13,422 (2586)	2033 (755)	1533 (1400)	**49,438** (21,479)	4120

■ **Table 4.** Patient Costs by Regimen and Service Category During 12 Months Following the First Chemotherapy Administration (or First-filled Prescription) of Second-line and Third-line Therapies

		Cost, Mean (SE), $								
Variable	No. of Patients	Chemotherapy Administration[a]	Emergency Department	Inpatient	Laboratory	Outpatient	Outpatient Rx	Skilled Nursing Facility	Total	Per Patient Per Month
Second-line therapy										
Docetaxel	149	11,877 (943)	1820 (410)	15,173 (2522)	582 (65)	20,669 (1766)	2494 (257)	919 (219)	**53,534** (3772)	4461
Pemetrexed disodium	31	23,667 (2427)	4084 (2024)	19,301 (10,666)	413 (81)	24,368 (4506)	1707 (356)	1770 (902)	**75,310** (13,334)	6276
Erlotinib hydrochloride	73	12,988 (1918)	883 (280)	5799 (1286)	220 (41)	9,678 (1524)	3888 (1462)	1576 (418)	**35,032** (3862)	2929
Other	385	11,816 (582)	1659 (309)	14,083 (1526)	659 (54)	21,733 (1211)	2863 (251)	906 (137)	**53,719** (2608)	4477
Third-line therapy										
Docetaxel	32	14,637 (3210)	1148 (566)	9325 (2734)	430 (117)	12,956 (2477)	3179 (1143)	1149 (597)	**42,824** (8079)	3569
Pemetrexed	28	22,989 (3473)	794 (357)	4800 (1159)	469 (108)	18,773 (3596)	2676 (609)	689 (276)	**51,190** (6654)	4266
Erlotinib	31	12,230 (2752)	986 (523)	10,725 (5291)	440 (130)	11,586 (2708)	1290 (287)	1818 (737)	**39,075** (8128)	3256
Other	155	8074 (967)	1686 (359)	13,623 (2410)	418 (58)	15,930 (1731)	2621 (364)	794 (155)	**43,146** (4043)	3596

[a]Includes injectable chemotherapy only.

were lowest for persons receiving erlotinib. These results are summarized in **Table 4**.

DISCUSSION

We conducted an analysis of patterns of utilization and costs of second- and third-line chemotherapy for patients with lung cancer from the perspective of a health insurer. We find that few patients receive second- and third-line therapy. In general, the lifetime costs of care for patients who receive chemotherapy do not vary substantially according to their initial regimen. Rather, what matters is whether they receive second- or third-line treatment. Monthly costs of care were substantially higher for those receiving second-line treatment and were still higher for patients receiving third-line chemotherapy compared with costs for those receiving only first-line treatment. Expenditures for all services (such as inpatient stays, outpatient visits, and emergency department visits) increased for these individuals. Therefore, the total costs may reflect more intensive management at all levels. Observation times were significantly longer for persons who received second- and third-line treatments compared with those who received only first-line treatment.

Several factors were significantly associated with the likelihood of receiving second-line therapy. As has been found in other population-based analyses of lung cancer therapy,[15,16] we find that older persons were somewhat less likely to receive second-line therapy. Increasing time between diagnosis and first-line therapy was associated with a lower likelihood of receiving second-line therapy. It is somewhat difficult to interpret this finding without clinical information, but delays in initiating first-line chemotherapy may be a marker of reduced physician or patient preference for chemotherapy in general or of clinical factors that delay the use of chemotherapy (eg, poorly controlled cardiovascular disease). Persons who received chemotherapy that included a platinum-containing agent (carboplatin or cisplatin) were less likely to receive second-line therapy than those who did not. Platinum-containing agents are recommended for first-line therapy[17] but are poorly tolerated. Therefore, those who receive them in this setting may be less likely to seek second-line therapy.

During the study period, the use of the tyrosine kinase inhibitors gefitinib and erlotinib grew substantially as agents for second- and third-line therapies, replacing a proportion of injectable chemotherapy agents. Erlotinib seems to have made substantial gains in utilization as a second- and third-line treatment for patients with lung cancer. Following FDA restrictions on the use of gefitinib, this drug is now all but removed from general use in this setting. It is likely that most

patients who were candidates for gefitinib are now being treated with erlotinib. It is unclear whether erlotinib is replacing other chemotherapy agents in order of treatment preference. It is clear that erlotinib is not being used substantially as a third-line agent for those who fail second-line therapy.

A modest proportion of patients who began chemotherapy received third-line chemotherapy. Most patients were given few administrations of third-line agents, and the intervals between administrations were irregular. This is understandable because survival is poor overall for patients with lung cancer, and it is likely that most patients who showed signs of progression after second-line treatment died before having the opportunity to receive third-line treatment or they or their physicians decided that the costs (monetary and treatment-related morbidity) of further treatment were not justified by the expected survival difference.

Limitations

The primary limitation of this analysis is the lack of clinical information. Although administrative claims are accurate in identifying persons who received chemotherapy,[9,18] claims cannot distinguish small cell and non–small cell lung cancer and cannot identify dates of death. Approximately 80% of incident lung cancers demonstrate non–small cell histologic findings, and the remainder are primarily of small cell type. Chemotherapy regimens differ for small cell and non–small cell lung cancer, although similar agents are commonly used for first-line treatment.[10,11]

Although the observation times were substantially longer for those receiving second- and third-line therapies, it is impossible to conclude that treatment resulted in greater survival. Selection effects could explain the difference; that is, those receiving additional treatments received them because they were in better health in general compared with those who did not receive second-line therapy. We can say that persons receiving second- and third-line regimens were treated much more intensively overall, as their PPPM costs were substantially higher during the observation periods.

Implications

Non–small cell lung cancer comprises approximately 80% of all lung cancer cases. During the period of this analysis, 4 agents (docetaxel, pemetrexed, gefitinib, and erlotinib) were approved for use as second-line therapy in patients with refractory non–small cell lung cancer. For small cell lung cancer that progresses after initial treatment, agents that have shown activity as second-line treatment include oral etoposide,

Take-away Points

There is disagreement about the best strategy for second-line and third-line chemotherapy regimens. Little is known regarding patterns of chemotherapy use and costs of care for persons who receive such treatment.

■ Our data suggest that a substantial fraction of chemotherapy use in second-line settings is not appropriate. This determination, combined with the finding of a wide variation in the use of agents, suggests a need for quality improvement.

■ Persons who received second-line chemotherapy that was not approved by the Food and Drug Administration had higher costs than persons who used approved therapies.

etoposide-cisplatin, cyclophosphamide-doxorubicin–vincristine sulfate, lomustine-methotrexate, paclitaxel, and topotecan hydrochloride.[19] Our data suggest that a substantial fraction of chemotherapy used in second-line settings is inconsistent with FDA labeling or is not supported by clinical studies. This determination, combined with the finding of wide variation in the use of agents, suggests a need for quality improvement. Of note, persons who received chemotherapy that is not FDA approved had higher costs than those who used approved therapies in the second-line setting, although the absolute difference (stated as PPPM cost) is modest overall.

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