Service Setting Impact on Costs for Bevacizumab-Treated Oncology Patients

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ABSTRACT

Objectives

To investigate treatment patterns and healthcare costs of patients with metastatic colorectal cancer (mCRC) or lung cancer (LC) who were treated with bevacizumab in a physician office (OFF) setting versus a hospital outpatient (HOP) setting.

Study Design

Retrospective analysis of claims from a national US health plan.

Methods

mCRC and LC patients initiating treatment with bevacizumab (index date) between January 1, 2006, and July 31, 2012, were identified. Patients were aged ≥18 years with ≥6-month pre- (baseline) and ≥6-month post index (follow-up) data, retaining patients who died with <6 months of follow-up. Differences by site of service were analyzed by χ^2 and *t* test (bevacizumab administrations, dose) and general linear model adjusted for demographic and clinical characteristics (all-cause healthcare costs).

Results

A total of 1687 mCRC (OFF: 1292; HOP: 395) and 1232 LC patients (OFF: 983; HOP: 249) were identified. Mean age was 61.3 years, 56.3% were male, and 78% were treated in OFF. Treatment in OFF declined from 2006 (84% of patients) to 2012 (61%). For OFF versus HOP, mean length of treatment (208.3 vs 191.0 days; $P = .007$), number of bevacizumab administrations per month (1.4 vs 1.1; $P < .001$), and mean weekly dose (eg, for 2012, 4.34 vs 3.11 mg/kg, $P < .05$) were higher in OFF. Adjusted monthly HOP costs (vs OFF) were higher by 37.8% for mCRC patients (cost ratio = 1.378; 95% CI, 1.282-1.482) and 31.1% for LC patients (cost ratio = 1.311; 95% CI, 1.204-1.427)

Conclusions

Despite fewer administrations and lower weekly dose of bevacizumab in HOP, adjusted total costs were 31% to 38% higher for mCRC and LC patients treated in the HOP setting.

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Cancer treatment has evolved considerably in the last 2 decades with the introduction of biological agents that target molecular pathways and improved surgical and radiation techniques.[1-3] There were an estimated 13.7 million cancer survivors in the United States in 2012 with a projection of 18 million by 2022.[4] Assuming only a 2% annual increase in medical costs in the first year after diagnosis and in the last year of life, the direct costs of cancer care based on Medicare claims are estimated to rise from $125 billion in 2010 to $173 billion in 2020.[5]

Controlling rising healthcare costs is a national priority. Medicare price reforms beginning in 2003 have effectively lowered reimbursement rates for physician-administered drugs, which are primarily chemotherapy agents.[6] Chemotherapy is a key treatment modality for many cancers, and patients typically receive chemotherapy in either a physician office setting or a hospital outpatient clinic. However, disparities in the acquisition costs of chemotherapy drugs—and thus, the income to providers—may have unintended consequences.[7] Hospitals eligible under the 340B program can obtain chemotherapy and other drugs at prices discounted up to 20% to 50%,[8] while community-based oncology clinics are not eligible for discounts.[7] Originally intended to assist hospitals serving vulnerable patients, 340B entities can obtain discounts on drugs for all eligible patients regardless of their insurance status or income.[7] The percentage of hospitals participating in 340B programs nearly tripled between 2005 and 2011.[8] A recent survey of community-based oncology practices suggests that some practices are closing,[9] referring patients to hospital outpatient clinics,[10] or being acquired or otherwise managed by a hospital entity.[9] The impact of a potential shift in site of chemotherapy administration warrants investigation to understand the economic implications.

There is a dearth of published literature comparing treatment patterns and costs in hospital outpatient versus physician office settings. Privately commissioned studies suggest that the cost of cancer care is higher in hospital outpatient

Take-Away Points

This study assessed bevacizumab treatment patterns and healthcare costs for patients with lung or colorectal cancer by setting of treatment initiation.

- Between 2006 and 2012, an increasing proportion of patients initiated treatment in hospital outpatient facilities rather than physician offices.
- The number of administrations and weekly doses were generally lower in hospital outpatient settings, yet healthcare costs were higher than in physician office settings.
- The shift in treatment setting for bevacizumab runs counter to programs attempting to retain patients in lower-intensity/lower-cost settings; these programs may need to account for the impact of market consolidation, reimbursement, and patient population changes.

clinics.[11,12] While these results provide an important overview of potential differences in costs depending on setting of chemotherapy administration, the studies did not control for important drivers of cost. For example, the selection of chemotherapy regimen is a function of multiple factors, including cancer type, stage, and patient clinical characteristics, and the cost of care will vary by regimen.

To investigate potential cost differences by site of administration, we focused on 2 of the most costly cancers: colorectal cancer and lung cancer,[5] and the use of bevacizumab[13] in the chemotherapy regimen. Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor and is approved for metastatic colorectal cancer and nonsquamous nonsmall cell lung cancer. The objective of this study was to investigate treatment patterns and costs of patients with metastatic colorectal cancer (mCRC) or lung cancer (LC) who were treated with bevacizumab in a physician office (OFF) setting versus a hospital outpatient (HOP) setting.

METHODS

Data Source and Design

This retrospective study used data from a large US healthcare claims database from July 1, 2005, through July 31, 2012 (patients were identified during the period January 1, 2006, through March 31, 2012, and the baseline period was the 6 months prior). Medical claims include *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*) diagnosis and procedure codes, Current Procedural Terminology procedure codes, Healthcare Common Procedure Coding System (HCPCS) procedure codes, site of service codes, provider specialty codes, and paid amounts. Pharmacy claims contain outpatient prescription pharmacy services including drug name, dosage form, drug strength, fill date, and dates of supply. Patients who died during the study were identified, and date of death was estimated based on a combination of hospital discharge status from medical claims, and month and year from the Social Security Administration master death file. Data were de-identified and accessed in accordance with Health Insurance Portability and Accountability Act privacy guidelines.[14]

Patients and Cohort Definition

Commercial and Medicare Advantage health plan members with medical and pharmacy benefits and evidence of bevacizumab treatment for either mCRC or LC were included. The index date was the earliest date of a claim for bevacizumab on or after January 1, 2006. Inclusion required: a) 2 claims (medical or facility claim) indicating receipt of bevacizumab (HCPCS codes C9214, C9257, J9035, S0116, Q2024) between January 1, 2006, and July 31, 2012; b) evidence of mCRC or LC; c) aged ≥18 years on the index date; and d) continuous enrollment for ≥6 months prior to the index date (baseline) and ≥6 months after the index date (follow-up). Patients with <6 months of follow-up due to death were included.

Evidence of mCRC required ≥2 claims with a diagnosis of colorectal cancer (CRC), *ICD-9-CM* 153.xx, 154.0, 154.1x, 154.8x, at least 30 days apart between 6 months prior to the index date (as early as July 1, 2005) and end of the study or health plan enrollment (as late as March 31, 2012), and ≥2 medical claims with a diagnosis of the same distant metastatic diagnoses (*ICD-9-CM* 196.0, 196.1, 196.3-196.9, 197.0-197.3, 197.7, 198.xx) at least 30 days apart during the same time period. Evidence of LC required ≥2 claims with a diagnosis of LC (*ICD-9-CM* 162.2-162.9) at least 30 days apart between 6 months before the index date and end of the study or health plan enrollment. Patients with claims for bevacizumab during baseline from an ophthalmology provider or >1 site of service (ie, physician office and hospital outpatient settings) were excluded. Patients with evidence of a primary cancer other than the index cancer (LC or CRC) were excluded if they had ≥2 claims for the same cancer type at least 30 days apart (based on 3-digit *ICD-9-CM* codes in the range 140.xx-195.xx, 199.xx-209.xx, excluding the codes for the index cancer type [LC or CRC and mCRC]). Patients with mCRC and evidence of another primary cancer were not excluded if the patient had a metastatic code for the same location (eg, if a patient had metastatic codes for the liver, the patient was not excluded if they also had a code for primary liver cancer).[15] Study cohorts were established based

on site of service codes where bevacizumab was administered: OFF or HOP.

MEASURES

Patient baseline characteristics included age (on index date), gender, insurance type, US census region, Quan-Charlson comorbidity score,[16] and presence of metastatic disease. Outcomes were determined during an episode of care (EOC) which began on the first bevacizumab infusion and ended at the earliest of: a) 30 days after the last infusion that occurred prior to a treatment gap of ≥3 months; b) death; c) disenrollment from the health plan; or d) end of the study (July 31, 2012). Outcomes were: number of bevacizumab infusions, the average weekly weight-based dose of bevacizumab (mg/kg/week), duration of therapy, all-cause monthly healthcare costs, and total costs on the day of bevacizumab infusion. The weight-based dose was estimated by dividing the weekly dose administered by the disease-specific population average weights for patients enrolled in clinical trials (data on file, Genentech, Inc). Duration of therapy was defined as the length of the EOC; discontinuation was a bevacizumab treatment gap of ≥3 months following the last infusion. Monthly healthcare costs were computed from the sum of health plan-paid and patient-paid amounts for medical and pharmacy claims. Medical costs were calculated by location of service on the claim, including office visits, hospital outpatient visits, emergency service, inpatient stays, and other costs. Costs per infusion day were computed from the sum of costs related to chemotherapy infusion on each day of bevacizumab administration, and included all drug and drug administration costs. Costs were adjusted to 2012 dollars using the annual medical care component of the Consumer Price Index.[17]

Statistical Analyses

Differences between the OFF and HOP cohorts for all measures were analyzed by χ^2 test (proportions) or 2-sided *t* test (continuous variables). The likelihood of discontinuation of therapy was modeled by Cox proportional hazards, and all-cause healthcare costs were modeled by a generalized linear model using a gamma distribution with a log link.[18] The models for the combined mCRC and LC population were adjusted for age, baseline Quan-Charlson comorbidity score,[15] and cancer type (mCRC or LC). Each cancer was modeled separately and contained the same adjustment variables except that cancer type was excluded.

RESULTS

Patient Selection and Characteristics

A total of 20,213 patients with at least 1 claim for bevacizumab during follow-up and no claims during baseline were identified (**Figure 1**). After applying inclusion and exclusion criteria, the final mCRC and LC study groups represented 1687 and 1232 patients, respectively. The most common reason for exclusion was lack of continuous health plan enrollment (n = 8524).

At baseline, the mean (SD) age of patients was 61.3 (11.2) years, 56.3% were men, and the mean (SD) comorbidity score was 6.62 (1.97) (**Table 1**). Study cohorts were similar for these characteristics. A higher proportion of HOP patients had evidence of metastatic disease at baseline than OFF patients. The majority of patients had commercial insurance but a higher proportion of LC patients had Medicare insurance versus commercial insurance in the HOP cohort.

Treatment Patterns

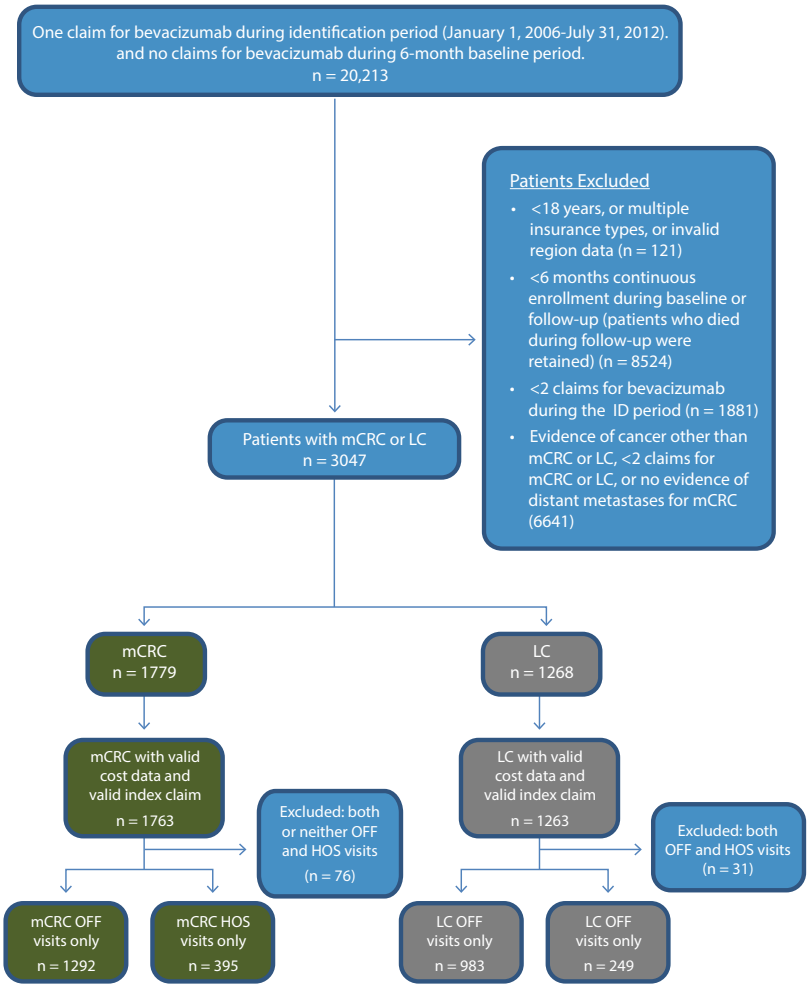
Over the entire study, the majority of mCRC (76.6%) and LC (79.8%) patients were treated in OFF settings (**Figure 2**). There was a pattern of an increasing proportion of patients treated at HOP sites over the course of the study for both mCRC and LC. The EOC was longer in the OFF vs HOP setting for mCRC patients (224.3 days vs 186.6 days, P <.001) but did not differ significantly for LC patients (187.3 days vs 197.9 days, P = .34) (**Table 2**). The number of bevacizumab infusions per EOC was greater at OFF sites than HOP sites for both mCRC (12.0 vs 7.5, P <.001) and LC (7.9 vs 6.9, P = .024). A similar pattern of significantly higher bevacizumab infusions per month was evident for both cancers at OFF versus HOP sites (P <.001). The mean weekly dose of bevacizumab on an estimated body weight basis (mg/kg) was significantly higher in the OFF setting for 3 of the 7 index years, and a similar trend was evident in all other years; mean weekly dose in the OFF setting ranged from 3.63 mg/kg in 2006 to 4.34 mg/kg in 2012, compared with 2.92 mg/kg in 2006 to 3.11 mg/kg in 2012 for the HOP setting (P <.05 in 2006, 2007, 2012, data not shown).

Patients with mCRC treated in HOP settings had 25.8% greater likelihood of discontinuing bevacizumab (hazard ratio [HR], 1.258; 95% CI, 1.115-1.419) than patients in the OFF setting. There were no differences in the likelihood of discontinuation for LC patients (HR, 0.908; 95% CI, 0.781-1.055) (data not shown).

Healthcare Costs

After multivariate adjustment for baseline patient characteristics, all-cause monthly healthcare costs were

Figure 1. Patient Selection



HOP indicates hospital outpatient setting; LC, lung cancer; mCRC, metastatic colorectal cancer; OFF, physician office setting.

higher by $6856, or 37.8%, for mCRC patients in HOP versus OFF settings (cost ratio, 1.378; 95% CI, 1.282-1.482; *P* <.001) and higher by $5983, or 31.1%, for LC patients in HOP settings (cost ratio, 1.311; 95% CI, 1.204-1.427; *P* <.001) (**Figure 3**). Unadjusted monthly all-cause costs followed a similar pattern of higher costs in the HOP setting for each cancer group (*P* <.001). The primary driver of actual costs was office-related costs for patients treated in the OFF setting (mCRC 78.7%; LC 75.4% of total costs) and outpatient costs for patients treated in the HOP setting (mCRC 88.5%; LC 85.9% of total costs). Higher monthly all-cause total costs at HOP sites were primarily a function of the difference between the dominant sources of costs: outpatient costs for HOP patients (mCRC, $22,903; LC, $22,898) and office costs for OFF patients (mCRC, $14,147; LC, $14,297) (*P* <.001 for HOP vs OFF in mCRC and LC). The cost for the entire duration of the EOC was: mCRC, $134,437 OFF versus $160,930 HOP; LC, $118,429 OFF versus $175,911 HOP (data not shown). The cost per infusion day was greater (*P* <.001) in the HOP than the OFF setting for both mCRC ($15,696 vs $6310) and LC ($18,307 vs $8510).

DISCUSSION

To our knowledge, this is the first study to compare treatment patterns and healthcare costs by site of chemotherapy administration specifically for mCRC and LC patients treated with bevacizumab. Our results suggest patients treated in the OFF setting receive more infusions of bevacizumab per month and per episode of care than patients treated in HOP settings. Although utilization of bevacizumab was greater in the OFF setting, adjusted monthly healthcare costs in HOP settings were 38% higher for mCRC patients and 31% higher for LC patients. There was a pattern of declining utilization of service at OFF sites and increasing utilization at HOP sites between 2006 and 2012.

The higher costs we observed in the HOP setting are consistent with unpublished reports. For Medicare patients with common cancers treated during 2006-2009, monthly allowed costs have been reported to be 14% higher at outpatient hospital sites.[11] Oncology patients with commercial insurance incurred 34% higher actual costs per chemotherapy episode in the HOP setting than patients treated in the OFF setting during 2008-2010.[12] Consistent with our results, the study of commercial patients noted higher per episode costs in the HOP setting despite shorter episode duration. In our study, despite shorter episode duration in the HOP setting, costs were higher per episode, per month, and per infusion day for patients treated in the HOP versus OFF setting.

For the entire study period, 78% of patients were treated at OFF sites, results which are comparable to reports based on commercial[12] and Medicare[11] patients treated in 2006 and later. However, the proportion of patients

Table 1. Baseline Demographic and Clinical Characteristics and Mortality During Follow-Up of Patients by Site of Service

	All patients			mCRC patients			LC patients		
	OFF (n = 2275)	HOP (n = 644)	*P*	OFF (n = 1292)	HOP (n = 395)	*P*	OFF (n = 983)	HOP (n = 249)	*P*
Characteristic	Mean (SD)			Mean (SD)			Mean (SD)		
Age, years	61.4 (11.0)	60.9 (11.8)	.311	60.1 (11.5)	59.6 (12.2)	.439	63.2 (10.0)	63.0 (11.0)	.810
Quan-Charlson comorbidity score	6.59 (2.00)	6.73 (1.84)	.120	7.08 (1.69)	7.12 (1.50)	.711	5.95 (2.19)	6.10 (2.15)	.326
	% (n)			% (n)			% (n)		
Male	56.7 (1289)	55.0 (354)	—	59.5 (769)	57.7 (228)	.559	52.9 (520)	50.6 (126)	.523
Insurance type			.008			.147			.010
Commercial	76.2 (1733)	71.0 (457)		78.5 (1014)	75.0 (296)		73.1 (719)	64.7 (161)	
Medicare	23.8 (542)	29.0 (187)		21.5 (278)	25.1 (99)		26.9 (264)	35.3 (88)	
US census region									
Northeast	4.7 (107)	18.9 (122)	<.001	4.3 (55)	15.4 (61)	<.001	5.3 (52)	24.5 (61)	<.001
Midwest	28.0 (194)	30.1 (194)	.299	28.1 (363)	31.4 (124)	.205	27.8 (273)	28.1 (70)	.937
South	55.1 (1253)	39.0 (251)	<.001	54.6 (705)	39.8 (157)	<.001	55.8 (548)	37.8 (94)	<.001
West	12.2 (278)	12.0 (77)	.892	13.2 (169)	13.4 (53)	.865	11.1 (109)	9.6 (24)	.569
Metastatic disease	38.5 (875)	49.7 (320)	<.001	49.0 (633)	58.7 (232)	<.001	24.6 (242)	35.3 (88)	<.001

HOP indicates hospital outpatient setting; LC, lung cancer; mCRC, metastatic colorectal cancer; OFF, physician office setting.

treated in the OFF setting tended to decline from a high of 84% in 2006 to a low of 61% by 2012. Our results suggest that the site of chemotherapy administration is shifting to HOP settings and that bevacizumab treatment patterns differ between OFF and HOP sites. In a study of Medicare patients during 2003-2006, no evidence of a change in site of chemotherapy administration was apparent.[19] Our study began in 2006, 3 years after the initial Medicare price reforms, which would allow more time for the impact of the reforms to be translated into practice. We do not know if the shift to HOP is specifically to 340B entities because claims data do not capture 340B status; however, the trend is consistent with this hypothesis.

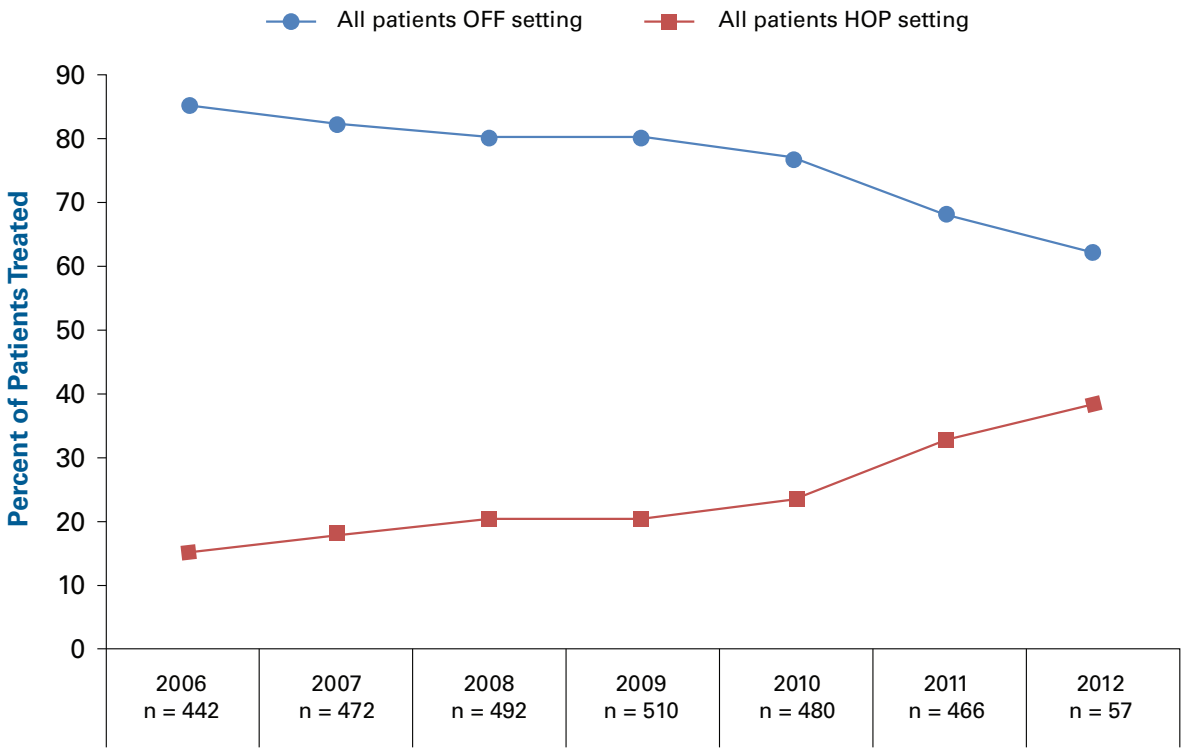
The differences in bevacizumab treatment patterns between OFF and HOP sites we observed are noteworthy. Patients receiving care in the OFF setting received a greater number of bevacizumab infusions and had longer episodes of care than patients treated in the HOP setting. The label for bevacizumab indicates that patients should be treated until progression. The reason for the shorter duration in the HOP setting is unknown as claims data do not provide clinical evidence of progression or adverse events that may have limited duration. However, for mCRC patients, the multivariate analysis results suggested that patients treated in the HOP setting were more likely to have their episode of care end due to discontinuation of treatment compared with patients in the OFF setting. The mean weekly dose of bevacizumab on an estimated body weight basis tended to rise during the course of the study at both sites but was generally higher in OFF settings. A change in prescribing patterns following the Medicare price reforms has been noted in previous studies of Medicare patients with lung cancer, including the use of chemotherapy agents with higher profit margins[20] and higher overall treatment rates.[6,20]

The impact of site of care on patient outcomes is largely unknown. The overall goal of treatment should be to optimize both outcomes and the efficiency of delivery of care. If outcomes are comparable between sites, our results suggest that there is an economic advantage for treating mCRC and LC patients in physician office sites. Recent recommendations for Medicare payment reform include delivery of care in a cost-efficient setting after accounting for potential differences in patient clinical severity.[21] Further research is needed to understand the potential impact of a shift in site of service on outcomes for patients with different primary cancers and clinical characteristics, as well as impact on patient quality of life and satisfaction with care.

Study Limitations

There are several limitations and the results should be considered in this context. Certain relevant clinical and disease-specific parameters that could affect outcomes are not available in claims data; these include, for example,

Figure 2. Percent of Patients Treated With Bevacizumab in Office and Hospital Outpatient Settings by Index Year



HOP indicates hospital outpatient setting; OFF, physician office setting.

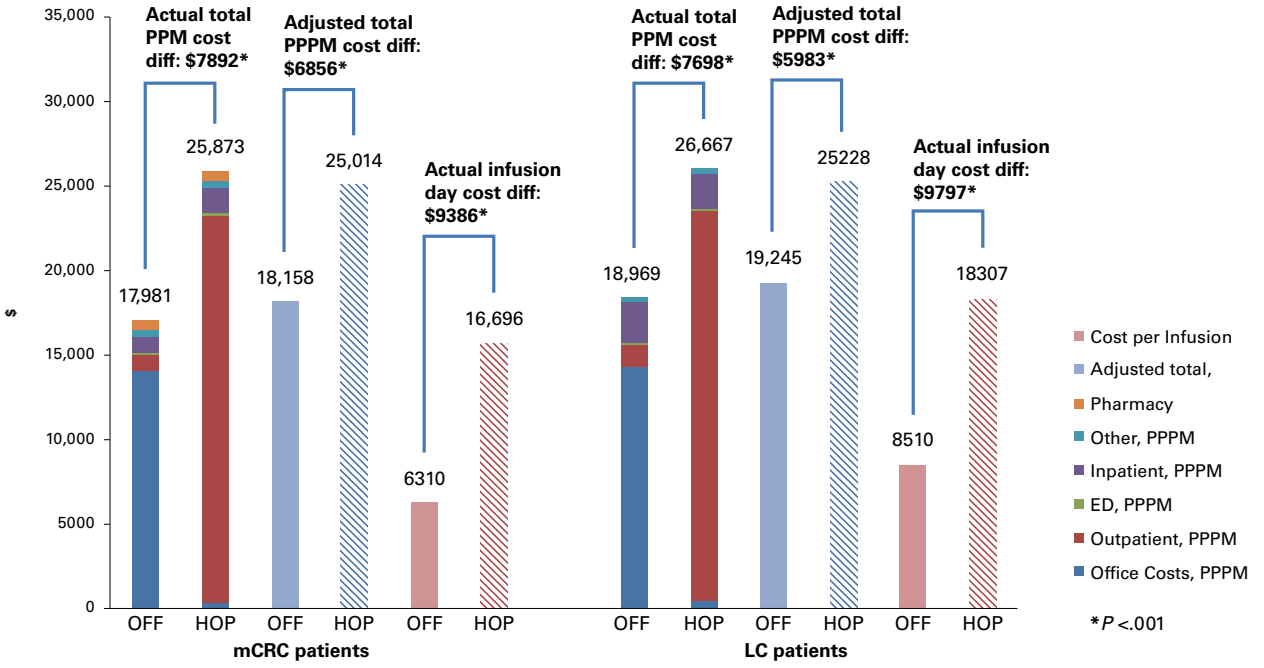
Table 2. Treatment Patterns by Site of Service

	All patients			mCRC patients			LC patients		
	OFF (n = 2275)	HOP (n = 644)	*P*	OFF (n = 1292)	HOP (n = 395)	*P*	OFF (n = 983)	HOP (n = 249)	*P*
Characteristic	Mean (SD)			Mean (SD)			Mean (SD)		
Length of EOC, days	208.3 (162.0)	191.0 (140.0)	.007	224.3 (166.6)	186.6 (125.3)	<.001	187.3 (153.4)	197.9 (160.5)	.335
Count of bevacizumab infusions									
Per episode of care	10.2 (8.8)	7.3 (6.1)	<.001	12.0 (9.4)	7.5 (6.0)	<.001	7.9 (7.1)	6.9 (6.2)	.024
Per month	1.4 (0.4)	1.1 (0.3)	<.001	1.6 (0.3)	1.2 (0.4)	<.001	1.2 (0.3)	1.0 (0.3)	<.001

EOC indicates episode of care; HOP, hospital outpatient setting; LC, lung cancer; mCRC, metastatic colorectal cancer; OFF, physician office setting.

the patient or physician rationale for receiving infusions either in the OFF or HOP setting, the selection of initial treatment regimen and any subsequent modifications based on patient performance status, and disease progression. The reason(s) for longer duration of treatment in the OFF setting is unknown. Changes to the label occurred during the course of the study, most notably an expansion of the indication for mCRC to include second-line treatment approximately 6 months after patient identification began; however, we would not expect label changes to have a differential impact on outcomes by site of service. The dose of bevacizumab was estimated from claims data, which are coded as the number of units of specific drug amounts (eg, 100 mg units). Thus, the dose administered was often recorded as the number of vials needed to dispense the appropriate dose, which could

Figure 3. Monthly Healthcare Costs and Cost per Infusion Day by Site of Service



Diff indicates difference; ED, emergency department; HOP, hospital outpatient setting; LC, lung cancer; mCRC, metastatic colorectal cancer; OFF, physician office setting; PPPM, per patient per month.

overestimate the dose administered (eg, a partially used vial was rounded up to a full vial). Further, body weight was not available and weight estimates from disease-specific population average weights for patients enrolled in clinical trials (data on file, Genentech, Inc) were used to estimate weekly dose per unit of body surface area. However, the calculations were applied uniformly in both the HOP and OFF setting so the degree of error in estimation would be expected to be consistent across settings. Some or all of the treatment received by patients enrolled in clinical trials may not generate insurance claims and may not have been included in this analysis. Finally, the data are from a managed care population and results may not apply to patients with other forms of insurance or the uninsured.

CONCLUSIONS

The majority of mCRC and LC patients received chemotherapy in OFF settings but the proportion of patients treated in OFF settings, generally declined over time. Although duration of treatment tended to be shorter and the weekly dose of bevacizumab lower in the HOP setting, total adjusted monthly costs were 38% higher for mCRC patients and 31% higher for LC patients treated in HOP settings.

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Authorship Information: Concept and design (NME-N, EBY, AS); acquisition of data (NME-N, LKB); analysis and interpretation of data (NME-N, EBY, LKB, AS); drafting of the manuscript (NME-N); critical revision of the manuscript for important intellectual content (NME-N, EBY, LKB); statistical analysis (LKB); obtaining funding (EBY); administrative, technical, or logistic support (AS); supervision (NME-N).

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