Survival and Lifetime Costs Associated With First-Line Bevacizumab Use in Older Patients With Metastatic Colorectal Cancer

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Key Words. Metastatic colorectal cancer • Bevacizumab • Elderly • Clinical effectiveness • Lifetime costs

ABSTRACT

Introduction. The objective of this study was to investigate clinical effectiveness and incremental lifetime costs associated with first-line bevacizumab in older patients with metastatic colorectal cancer (mCRC).

Methods. Patients diagnosed with mCRC in 2004–2007 were identified from the Surveillance, Epidemiology, and End Results–Medicare database and stratified by first-line treatment (no chemotherapy [CTx], CTx alone, CTx plus bevacizumab). The impact of first-line bevacizumab on survival was investigated using a propensity score adjusted multivariate Cox proportional hazards model. Mean lifetime costs for each cohort were calculated using Medicare claims for all services rendered between diagnosis and end of follow-up, adjusting for death and censoring.

Results. A total of 4,414 patients (mean age: 77.3 years) were identified, of whom 15% received first-line bevacizumab. Among first-line-treated patients, bevacizumab receipt was

associated with improved overall survival (hazard ratio: 0.85 [95% confidence interval: 0.75–0.97]; $p = .013$), and this benefit was limited to patients who received >1 month of bevacizumab therapy. Median and mean survival were greatest in patients treated with CTx plus bevacizumab relative to CTx alone (CTx plus bevacizumab median 19.4 months [mean 28.0 months] vs. CTx alone median 15.1 months [mean 22.9 months]; $p < .001$), as were mean lifetime costs (mean per patient cost \$143,284 vs. \$111,280). Compared with CTx alone, CTx plus bevacizumab was associated with a 5.1-month increase in mean survival and a \$32,004 increase in mean lifetime treatment costs, with an incremental cost of \$75,303 per life-year gained.

Conclusion. Bevacizumab use is associated with longer survival than CTx alone in older patients treated in real-world clinical settings, at an incremental cost of \$75,303 per life-year gained. *The Oncologist* 2014;19:892–899

Implications for Practice: As new effective and expensive oncology drugs emerge and contribute to the rapid rise in cancer treatment costs in the U.S., it is important for clinicians and policy makers to understand the relative benefits and costs of these drugs in real-world clinical practice. The use of bevacizumab in the initial treatment of a population-based sample of older patients with metastatic colorectal cancer is associated with improved survival beyond initial chemotherapy alone, at an incremental cost of approximately \$75,000 for every life-year gained. Although older patients treated in the community may benefit from bevacizumab, Medicare will likely face significant challenges in sustaining the costs associated with expensive new drugs in an aging population.

INTRODUCTION

The improvement in overall prognosis for patients with metastatic colorectal cancer (mCRC) over the last decade can be attributed, in part, to the approval of several new chemotherapeutics and biologics. First-line treatment with bevacizumab, for example, has been shown in randomized clinical trials to improve median survival by approximately 4 months [1]. Median survival estimates from first-line trials have approached and, in some cases, exceeded 2 years [2–6].

The cost of mCRC treatment has also increased substantially over this same time period. Drug costs alone for first-line therapy are now 100-fold greater than in the days of single-agent 5-fluorouracil (5-FU) [7–9]. As newer agents are added to existing chemotherapy (CTx) backbones, the cumulative lifetime costs of treating mCRC continue to rise.

The rising cost of cancer treatment is of particular concern to Medicare, the primary payer of health services for persons

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aged 65 years and older. Cancer-related costs compose a growing proportion of Medicare spending, which is projected to increase exponentially over the next decade [10–12]. Although Medicare coverage and reimbursement decisions are not informed by cost and cost-effectiveness analyses, it is still important in an era of rising health care spending to consider the relative costs and benefits of newer agents in an older patient population. Clinical trial data, which form the basis of coverage decisions, may not translate to the Medicare population (aged ≥ 65 years). The median age of CRC diagnosis, for example, is 70 years based on estimates from the Surveillance, Epidemiology, and End Results (SEER) database (2004–2008), whereas the median age of patients enrolled in many landmark first-line mCRC clinical trials is 60 years [1, 3, 13–16]. In contrast, drug costs are fixed regardless of age. Older patients may also face additional costs related to adverse events and hospitalizations. Consequently, assessment of costs and benefits may be particularly important in older patients with underlying comorbidities in whom the cost-to-benefit ratio may be less favorable than for younger individuals.

Previous studies using SEER-Medicare data have suggested that the median survival for older mCRC patients is improving over time and that bevacizumab confers a modest survival benefit in this population [17, 18]. In a pooled efficacy analysis of older patients enrolled in two randomized clinical trials, bevacizumab was associated with improved survival compared with CTx alone (19.3 vs. 14.3 months, $p = .006$) [19]. A recent randomized phase III study in patients aged 70 and older (AVEX trial) demonstrated a benefit in progression-free survival (hazard ratio [HR]: 0.53; 95% confidence interval [CI]: 0.41–0.69) with the addition of bevacizumab to single-agent capecitabine [20]. Still, the survival impact of various CTx regimens and bevacizumab in first- and subsequent-line treatment in older mCRC patients is not well understood.

Few studies have reported on the relative costs and benefits of first-line bevacizumab treatment, and none have been conducted from the perspective of the U.S. health care system. A recent study from England and Wales reported an incremental cost-effectiveness ratio of £62,857 (\$93,814 in 2013 dollars) per quality-adjusted life-year (QALY) when bevacizumab was added to the combination of irinotecan, 5-Fluorouracil, and leucovorin and £88,436 (\$131,990) per QALY when bevacizumab was added to first-line 5-FU/leucovorin [21]. Previous studies that have explored the economic burden of mCRC in older adults using SEER-Medicare data have focused on costs by treatment phase or lifetime costs relative to noncancer controls [22]. To our knowledge, no studies have investigated the differences in lifetime treatment costs and clinical benefit of first-line treatment strategies in mCRC.

The objective of this analysis was to estimate benefits and lifetime costs of first-line chemotherapy with bevacizumab relative to chemotherapy alone in older mCRC patients treated in community clinical settings.

MATERIALS AND METHODS

Data Source

The source of data for this study was the National Cancer Institute's merged SEER-Medicare database, which links SEER

data on cancer diagnoses and survival to claims for covered medical services for Medicare enrollees [23–25]. Local SEER registries represent approximately 28% of the U.S. population; the combined SEER-Medicare database includes claims for approximately 94% of patients aged 65 and older diagnosed with cancer in one of the SEER regions [24]. In early 2011, the SEER-Medicare linkage was updated to include SEER cancer diagnoses through 2007 with Medicare claims through December 31, 2009.

Patient Selection

Patients were included in the study if they were diagnosed with de novo metastatic (stage IV, based on the American Joint Committee on Cancer Staging Manual [26]) adenocarcinoma of the colon, rectosigmoid colon, or rectum between January 1, 2004, and December 31, 2007 [24]. The primary analysis was limited to the 2004–2007 time period to capture patients treated in the bevacizumab era (bevacizumab was approved by the U.S. Food and Drug Administration in 2004). Patients were excluded if they were aged < 65 years, were diagnosed with end-stage renal disease, qualified for Medicare as a result of disability, lacked Medicare parts A and B in the 12 months before and after diagnosis, were ever diagnosed with another primary cancer, or did not have histologically confirmed disease. Because the Centers for Medicare and Medicaid Services (CMS) do not require submission of individual claims for services by Medicare health maintenance organizations (HMOs), patients who were enrolled in a Medicare HMO in the 12 months before and after diagnosis were excluded [27]. Finally, patients for whom the diagnosis of mCRC was made by death certificate, by autopsy, or in the same month as death were excluded. Patients were followed from the time of diagnosis until death or until the last date of available Medicare claims (December 31, 2009).

Identification of Patient Characteristics

Demographic factors thought to potentially influence treatment patterns and survival (age, race, sex) were identified from SEER. Noncancer comorbidity was determined using the Klabunde comorbidity score, based on the presence of International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) diagnosis codes for 13 comorbidities in the 12 months prior to diagnosis [28–30]. Receipt of hepatic metastatectomy was also identified using ICD-9-CM and CPT category 3 codes for partial lobectomy, trisegmentectomy, and total left or total right lobectomy anytime from diagnosis until end of follow-up [17].

Identification of First-Line Treatment Cohort

Medicare claims can be used to identify CTx utilization in colorectal cancer with good sensitivity [31]. First-line treatment was defined as CTx receipt within 3 months of diagnosis, identified by generic CTx administration, diagnostic, and procedural codes as well as J codes for specific agents (5-fluorouracil, capecitabine, oxaliplatin, irinotecan, bevacizumab, cetuximab, panitumumab). Patients were considered to have received bevacizumab only if its specific J code could be identified. If no CTx claims were present within 3 months of diagnosis, then patients were considered not to have received first-line CTx. Patients were divided into three first-line

treatment cohorts (no CTx, CTx alone, and CTx plus bevacizumab).

For all patients who received first-line CTx (with or without bevacizumab), the “backbone” CTx regimen was determined based on claims for all CTx drugs within the first 3 months after diagnosis. If a patient had a claim, for example, for both 5-FU and oxaliplatin within 3 months of diagnosis, they were considered to have received these drugs in combination. Subsequent use of bevacizumab or an EGFR inhibitor (cetuximab or panitumumab) was identified in patients who did not initially receive bevacizumab in first-line treatment. Duration of first-line bevacizumab was defined as the time elapsed between the first claim for bevacizumab within 3 months of diagnosis and the last claim for bevacizumab before a gap of 90 days or longer in bevacizumab claims.

Identification of Lifetime Costs

Lifetime treatment costs were determined using all Medicare claims (payments) for services rendered from diagnosis until death or end of follow-up. Cost estimates were presented in 2004 dollars with an annual discounting rate of 3% for future years [32]. Costs were grouped by the type of associated claim: CTx costs, surgery, radiation, imaging, hospitalizations (including emergency room visits and skilled nursing facility stays), interventional radiology, office visits, and other costs not falling into one these specified categories.

Data Analysis

Summary statistics were used to describe basic characteristics of the study population (race, age, sex, and Klabunde comorbidity index) as well as treatment patterns (frequency of hepatic resection, first-line CTx use, subsequent use of bevacizumab or EGFR inhibitor, bevacizumab treatment duration, and CTx backbone).

Kaplan-Meier methods were used to determine median survival stratified by first-line treatment cohort. Log-rank tests for equality of survivor functions were used to test for differences in survival between first-line cohorts. Mean survival was also determined for each cohort after exponentially extending the survival curve to zero for censored cases. To further investigate the impact of first-line treatment on survival, a Cox proportional hazards model was used to compare the relative risk of death between patients treated with CTx plus bevacizumab versus CTx alone, adjusting for various factors thought to influence risk of death (age, race, sex, comorbidity score, hepatic resection). To address the issue of potential confounders and selection bias influencing first-line treatment choice, a propensity score matched analysis was performed. In this analysis, propensity scores were calculated using the same variables noted above, and patients in the CTx alone and CTx plus bevacizumab cohorts were matched by propensity score. This propensity score matched sample was then used to fit the propensity score-adjusted Cox model. Given that patients who receive first-line bevacizumab may receive the drug for variable durations, a Cox proportional hazards model with bevacizumab receipt as a time-dependent covariate was also performed.

Total lifetime costs were determined for patients diagnosed in 2004–2007 stratified by first-line treatment cohort using the Kaplan-Meier cost estimator, which sums the Kaplan-

Meier probability of surviving to the beginning of each month multiplied by the mean costs for patients alive at the beginning of each month [33, 34]. The Kaplan-Meier cost estimator is useful in cases in which a substantial percentage of patients are censored. This method avoids bias associated with limiting cost estimation only to patients who have died during follow-up (cost estimates based largely on patients with shorter survival times) or to determining average costs for all patients in the sample (underestimates cost by not accounting for costs incurred after censoring). Across all cost categories, lifetime mean and median costs were determined. For patients who live at least 12 months from diagnosis, mean costs were determined for each month after diagnosis and were represented graphically as trends in spending in the first year.

Differences in mean lifetime treatment costs and mean survival were calculated for patients receiving CTx plus bevacizumab versus CTx alone and no CTx; incremental cost-effectiveness ratios (incremental lifetime cost per life-year gained) were presented. A similar analysis was conducted in the subset of patients aged ≥ 75 years, given that patients of this age group are not routinely enrolled in clinical trials and the incremental costs and benefits in this group may be different than those of the larger population aged ≥ 65 years.

RESULTS

Patient Characteristics and Treatment Patterns

A total of 4,414 patients were diagnosed in 2004–2007 (mean age: 77.3 years), of whom 15% received bevacizumab in first-line therapy (Table 1). A total of 2,687 (61%) of all patients diagnosed in this time period were aged 75 years or older, and the majority (70%) did not receive CTx within 3 months of diagnosis. A relatively small proportion of patients (5%) received hepatic resection, although a greater proportion of patients who received CTx (alone or with bevacizumab) underwent hepatic resection compared with patients who did not receive first-line CTx ($p < .001$). Among first-line-treated patients, the most common CTx backbones were oxaliplatin-containing combinations (FOLFOX or CAPOX) (Table 1).

Among patients who received first-line bevacizumab, mean duration of bevacizumab receipt was 6.9 months. A total of 421 patients (39%) who received first-line CTx alone went on to receive bevacizumab later on during the course of treatment. Use of EGFR inhibitors (cetuximab or panitumumab) in subsequent lines of therapy was greater among patients receiving first-line CTx with bevacizumab compared with CTx alone (39% vs. 28%, $p < .001$). Mean duration of subsequent therapy with panitumumab and cetuximab was similar across both cohorts (Table 1).

First-Line Treatment Cohort and Survival

A multivariate Cox proportional hazards model was used to explore differences in survival between patients receiving CTx alone versus CTx plus bevacizumab in 2004–2007, adjusting for several underlying factors that might have influenced the initial choice of first-line regimen (age, sex, race, comorbidity, hepatic resection) (Tables 2, 3). Receipt of bevacizumab (HR: 0.77; 95% CI: 0.70–0.85; $p < .001$) and hepatic resection (HR: 0.35; 95% CI: 0.29–0.41; $p < .001$) were both associated with improved survival. In contrast, age ≥ 75 years was associated

Table 1. Demographic and treatment characteristics by first-line treatment cohort (diagnosis 2004-2007)

Characteristics	No CTx (n = 2,679)	CTx alone (n = 1,092)	CTx plus Bev (n = 643)
Sex, n (%)			
Male	1,216 (45)	583 (53)	328 (51)
Female	1,463 (55)	509 (47)	315 (39)
Race, n (%)			
White	2,149 (80)	927 (85)	557 (87)
Nonwhite	530 (20)	165 (15)	86 (13)
Age, n (%)			
<75 years	786 (29)	577 (53)	364 (57)
≥75 years	1,893 (71)	515 (47)	279 (43)
Klabunde index, n (%)			
<1	1,627 (66)	815 (81)	482 (80)
≥1	825 (34)	195 (19)	117 (20)
CTx backbone, n (%)			
5-FU/Cap alone	NA	324 (30)	91 (14)
5-FU/Cap plus Ox	NA	335 (31)	363 (56)
5-FU/Cap plus Iri	NA	101 (9)	86 (13)
Iri alone or Iri plus Ox	NA	13 (1)	7 (1)
Other	NA	319 (29)	96 (15)
Hepatic resection, n (%)			
Yes	90 (3)	86 (8)	57 (9)
Subsequent Bev receipt, n (%)			
Yes	346 (13)	421 (39)	NA
Subsequent EGFR inhibitor receipt, n (%)			
Cetuximab	151 (6)	266 (24)	221 (34)
Panitumumab	27 (1)	44 (4)	32 (5)
Mean duration of subsequent antibody therapy (months)			
Bev	8.70	9.60	NA
Cetuximab	4.51	4.03	3.99
Panitumumab	2.15	3.45	2.19

Percentages included in parentheses are proportions of the column total. Abbreviations: 5-FU, 5-fluorouracil; Bev, bevacizumab; Cap, capecitabine; CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; Itr, irinotecan; Ox, oxaliplatin.

with poorer survival (HR: 1.26; $p < .001$). In the propensity score matched analysis, 597 patients receiving CTx plus bevacizumab were matched to 597 patients receiving CTx alone by propensity score, which was calculated using the same variables included in the standard Cox model (age, sex, race, comorbidity, hepatic resection). When fitting the propensity score-adjusted model to this propensity score matched sample, receipt of bevacizumab was still associated with improved survival compared with CTx alone, although to a slightly lesser magnitude (HR: 0.85; 95% CI: 0.75–0.97; $p = .013$) (Tables 2, 3).

Given that patients in the CTx plus bevacizumab cohort do not initiate bevacizumab at the same time and do not receive bevacizumab for uniform durations, survival by first-line treatment cohort was explored with bevacizumab as a time-dependent covariate. In general, CTx plus bevacizumab receipt of any duration was associated with improved survival compared with CTx alone (HR: 0.80; 95% CI: 0.72–0.88;

$p < .001$). After recategorizing bevacizumab by duration of therapy received (none, ≤1 month, 1–3 months, 3–6 months, >6 months), only patients who received >1 month of treatment experienced a survival benefit, whereas patients receiving ≤1 month of bevacizumab actually experienced poorer survival than patients receiving CTx alone (HR: 1.57; 95% CI: 1.25–1.97; $p = .002$) (Tables 2, 3).

Unadjusted median survival by Kaplan-Meier estimate was longest in patients who received first-line CTx plus bevacizumab (19.4 months; 95% CI: 10.2–33.4) compared with patients receiving CTx alone (15.1 months; 95% CI: 6.9–29.4) or no CTx (5.7 months; 95% CI: 2.3–16.0) (Table 4). The survival differences observed among the three first-line treatment cohorts were significant by log-rank test ($p < .001$). The same statistically significant trend in survival was seen among the oldest patients (aged ≥75 years) ($p < .001$).

Lifetime Treatment Costs

Mean lifetime costs per patient were greatest among patients receiving CTx plus bevacizumab (\$143,284 per patient) (Fig. 1). In the subset of patients aged ≥75 years, spending was also greatest in the CTx plus bevacizumab cohort, although lower than seen in the larger population (\$117,218 per patient) (Fig. 1). Differences in mean monthly spending among the three cohorts was greatest at approximately 3 months from diagnosis; these differences seemed to resolve by approximately 8 months after diagnosis (Fig. 1).

Spending for hospitalizations, emergency room or urgent care visits, and skilled nursing facilities composed the greatest proportion of spending for patients who did not receive CTx or received CTx alone. CTx and targeted therapy costs comprised the greatest proportion of spending (48%) for patients in the CTx plus bevacizumab cohort. Among patients who did not receive CTx within the first 3 months after diagnosis, subsequent CTx receipt was associated with a mean lifetime cost per patient of \$8,835 (Table 4).

Incremental Cost Effectiveness: Relative Costs Versus Relative Benefit of Bevacizumab

The differences in lifetime mean costs for patients treated with CTx plus bevacizumab compared with patients treated with CTx alone and no CTx were \$32,004 and \$90,780, respectively. The corresponding differences in mean survival were 5.1 months and 13.9 months, respectively. Compared with CTx alone, first-line CTx plus bevacizumab was associated with an incremental cost of \$75,303 per life-year gained.

Among patients aged ≥75 years, differences in lifetime mean costs for CTx plus bevacizumab-treated patients compared with patients treated with CTx alone and no CTx were \$28,429 and \$71,320, respectively. The corresponding differences in mean survival were 3.9 months and 11.8 months, respectively. Compared with CTx alone, first-line CTx plus bevacizumab was associated with an incremental cost of \$87,473 per life-year gained.

DISCUSSION

Using SEER-Medicare data, we determined the relative survival benefit of different first-line treatment strategies in older patients, along with the incremental lifetime diagnosis and treatment costs. Our findings suggest that first-line bevacizumab

Table 2. Multivariate Cox proportional hazards model and propensity score matched analysis showing survival for chemotherapy plus bevacizumab

Variable ^a	Standard model			Propensity score adjusted model		
	HR	95% CI	p value	HR	95% CI	p value
Bevacizumab receipt	0.77	(0.70–0.85)	<.001	0.85	(0.75–0.97)	.013
Age	1.26	(1.16–1.36)	<.001	1.21	(1.04–1.41)	.015
Race	1.09	(0.98–1.22)	.116	1.07	(0.89–1.28)	.474
Sex	1.04	(0.96–1.13)	.301	1.01	(0.89–1.14)	.915
Klabunde comorbidity index	1.14	(1.04–1.26)	.006	1.13	(0.97–1.33)	.113
Hepatic resection	0.35	(0.29–0.41)	<.001	0.44	(0.33–0.60)	<.001

^aReference categories: Chemotherapy alone (no bevacizumab), age <75 years, nonwhite race, female sex, Klabunde index <1, no hepatic resection. Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 3. Multivariate Cox proportional hazards model and propensity score matched analysis showing survival for chemotherapy with bevacizumab as a time-dependent covariate

Bevacizumab duration ^a	Median survival (months)	95% CI	HR	95% CI	p value
≤1 month	6.5	(5.5–9.6)	1.57	(1.25–1.97)	.002
1–3 months	16.8	(14.4–23.5)	0.70	(0.56–0.88)	<.001
3–6 months	23.7	(19.1–27.9)	0.61	(0.51–0.74)	<.001
>6 months	23.3	(20.3–25.9)	0.81	(0.69–0.94)	.008
Age			1.26	(1.17–1.37)	<.001
Race			1.09	(0.97–1.22)	.135
Sex			1.04	(0.96–1.12)	.333
Klabunde comorbidity index			1.15	(1.04–1.27)	.006
Hepatic resection			0.34	(0.29–0.41)	<.001

^aReference categories: No bevacizumab (chemotherapy alone), age, 75 years, nonwhite race, female sex, Klabunde index, 1, no hepatic resection. Abbreviations: CI, confidence interval; HR, hazard ratio.

is associated with a significant median survival benefit (4.3 months) in older patients compared with CTx alone, including in the oldest subset of patients (2.6 months in patients aged ≥75 years). As expected, the addition of bevacizumab to first-line therapy is associated with an increase in mean lifetime treatment costs. The incremental mean per-patient cost for each additional month of survival with the addition of bevacizumab was \$6,275 in all patients and \$7,289 in patients aged ≥75 years. Average sales price (ASP) per month of bevacizumab treatment (drug costs alone) in a 70-kg individual is \$4,449 (2013 ASP) [35]. The incremental difference in mean monthly per-patient treatment cost is higher than the per-month cost of bevacizumab, possibly due to differences in CTx backbones, CTx administration costs, subsequent use of EGFR inhibitors, or imaging in the CTx plus bevacizumab group compared with the CTx alone group. We did observe slightly higher use of subsequent EGFR inhibitors in the CTx plus bevacizumab group compared with the CTx alone group, and this may explain at least a portion of the significant gap in mean lifetime costs between these cohorts. We also found that the benefit of CTx plus bevacizumab relative to CTx alone was limited to patients who received >1 month of treatment with bevacizumab. Early discontinuation of bevacizumab in this population was likely a marker of either quickly progressive disease or a bevacizumab-related adverse event, both of which could be associated with generally poorer

prognosis. Our findings are particularly relevant, given the burden that rapidly rising cancer treatment costs is placing on Medicare and the health care system at large. Clinicians should be aware of treatments that are prohibitively expensive and that provide minimal benefit in an older patient population. In the first-line setting, bevacizumab seems to be effective in a real-world population of older adults and is associated with an acceptable cost-effectiveness ratio. Although cost-effectiveness thresholds are not clearly established in the U.S., there is some acceptance that a treatment is cost effective if it falls within or below a threshold of \$50,000 to \$150,000 per QALY [36, 37]. At \$75,303 per life-year gained, first-line bevacizumab seems to be cost effective at this threshold. Although we did not calculate QALYs gained, first-line bevacizumab would still fall below accepted cost-effectiveness thresholds if we were to attribute a health utility of 0.8 to colon cancer (\$94,129 per QALY) [21, 38].

In considering these findings, several limitations should be mentioned. First, although the majority of costs for services rendered can be captured through SEER-Medicare, costs associated with outpatient prescriptions through Medicare Part D were not captured. Prescriptions associated with complications from bevacizumab (e.g., low-molecular-weight heparin for thrombotic event) and/or CTx are not captured in this analysis. Consequently, we may have underestimated the lifetime costs in the bevacizumab-treated

Table 4. Median survival, mean survival, and mean lifetime costs by treatment category

Variable	No CTx (n = 2,679)	CTx alone (n = 1,092)	CTx plus Bev (n = 643)
Survival, ^a median (95% CI)			
All patients	5.7 (2.3–16.0)	15.1 (6.9–29.4)	19.4 (10.2–33.4)
Patients aged ≥75 years	5.1 (2.1–13.6)	13.6 (5.7–25.6)	16.2 (8.7–28.3)
Survival, mean			
All patients	14.1	22.9	28.0
Patients aged ≥75 years	12.4	20.3	24.2
Cost category, \$ (%)			
All CTx	8,835 (17)	38,370 (34)	68,789 (48)
CTx, administration ^b	1,090 (2)	5,556 (5)	7,508 (5)
CTx, Bev ^b	3,224 (6)	10,318 (9)	29,865 (21)
CTx, non-Bev ^b	4,520 (9)	22,496 (20)	31,417 (22)
All surgery	1,142 (2)	3,411 (3)	4,220 (3)
Surgery, endoscopic	166 (<1)	298 (<1)	330 (<1)
Surgery, other	976 (2)	3,113 (3)	3,891 (3)
Radiation	477 (18)	1,466 (1.3)	964 (<1)
Imaging	1,672 (3)	4,478 (4)	5,787 (8.4)
Hospitalization, ER/urgent care, skilled nursing facility	34,749 (66)	44,887 (40)	41,681 (29)
Interventional radiology	59 (<1)	248 (<1)	411 (<1)
Office visits	1,004 (2)	2,594 (2)	3,054 (2)
Other costs	4,566 (9)	15,825 (14)	18,377 (13)
Total costs	52,504	111,280	143,284

^aLog-rank test for equality of survivor functions between cohorts: chi-square: 165.63, $p < .001$.

^bCTx or Bev administration and drug costs for patients in the “no CTx” and “CTx alone” cohorts refer to CTx or Bev use after 3 months from diagnosis. Percentages included in parentheses are proportions of the column total.

Abbreviations: Bev, bevacizumab; CI, confidence interval; CTx, chemotherapy; ER, emergency room.

patients. Next, the survival differences observed among the three first-line treatment cohorts may be due to factors that led to the first-line treatment recommendation in the first place rather than the treatment itself. Patients who receive CTx alone, for example, may have had other comorbidities such as cerebrovascular disease or thrombosis that led to the decision not to use bevacizumab. A survival benefit with bevacizumab was seen in a Cox proportional hazards model designed to adjust for underlying comorbidity, age, and other factors. Nonetheless, there may be other factors not included in SEER-Medicare (e.g., Eastern Cooperative Oncology Group performance status) that could explain these survival differences and that could not be accounted for in the Cox model. We attempted to account for confounding using a propensity score-adjusted model; however were limited in the variables available to use in calculation of the propensity scores. Similarly, costs associated with hospitalizations and urgent care and emergency room visits may be relatively higher in patients treated with CTx alone if these patients were more likely to have serious comorbidities that limited utilization of bevacizumab. Finally, the Kaplan-Meier cost estimator takes into account all costs incurred over the course of a patient's lifetime, including costs associated with subsequent treatments. As such, subsequent therapies are likely to have an impact on overall lifetime treatment costs in a cohort. We observe a small but significant increase in the use of subsequent EGFR inhibitors in the CTx plus bevacizumab cohort compared with the CTx

alone cohort. In contrast, subsequent bevacizumab use is seen in nearly 40% of the CTx alone cohort. This practice of exposure to multiple targeted agents across the continuum of CRC treatment reflects the standard of care. Given the relatively long median survival and frequent use of subsequent-line monoclonal antibodies in both groups, it is not likely that these differences in subsequent therapies were solely responsible for the observed differences in mean lifetime costs or median survival between the CTx alone and CTx plus bevacizumab cohorts. Despite these limitations, our study puts relative cost in the context of relative benefit for patients treated in real-world clinical settings. Previous studies that have used SEER-Medicare to investigate lifetime costs of treatment have focused on the relative lifetime costs for cancer patients versus noncancer controls or have examined cost trends over time by initial, continuing, and terminal-phase costs [22, 39–44]. This study is one of the few to examine differences in lifetime mean costs by first-line treatment cohort [45, 46].

CONCLUSION

Using SEER-Medicare data, we found that first-line bevacizumab is associated with a significant improvement in survival compared with CTx alone in older patients, after controlling for various factors that might influence first-line treatment recommendations and outcome. As expected, the addition of bevacizumab to first-line therapy is associated with an increase in lifetime treatment costs, with an incremental cost

Figure 1. Mean lifetime metastatic colorectal cancer treatment costs (**A**) and mean monthly per patient spending in the first 12 months following diagnosis (**B**). Costs are payments by Medicare to service providers and are in 2004 dollars with 3% discounting per year. Abbreviations: Bev, bevacizumab; CTx, chemotherapy; mCRC, metastatic colorectal cancer.

of \$75,303 per life-year gained. Our findings suggest that first-line bevacizumab in older patients is clinically effective at a cost that falls within generally accepted boundaries in the U.S. (\$50,000 to \$100,000 per QALY). Further investigation into the relative benefit and relative cost of bevacizumab in subsequent lines of therapy will be interesting, given recent data supporting its use after progression through first-line bevacizumab. The relative costs and benefits of EGFR inhibitors should also be considered, although first-line use of these drugs is very minimal in the current dataset. Subsequent SEER-Medicare data linkage updates can be used to answer these questions.

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DISCLOSURES

David Mummy, Lisel Koepl: Genentech, Inc. (RF); **Veena Shankaran:** Genentech Inc., Lilly (RF); **Elaine Yu:** Genentech (E); Roche (OI); **Robert Morlock:** Genentech (E); **Scott D. Ramsey:** Genentech (C/A); **Sarika Ogale:** Genentech (E); Roche (OI). The other authors indicated no financial relationships.

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