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ORIGINAL REPORT

Effectiveness of Bevacizumab With First-Line Combination Chemotherapy for Medicare Patients With Stage IV Colorectal Cancer

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ABSTRACT

Purpose
Clinical trials have shown that adding bevacizumab to cytotoxic chemotherapy improves survival for patients with colorectal cancer, although its effectiveness in the Medicare population is uncertain.

Patients and Methods
Using the Surveillance, Epidemiology, and End Results (SEER) -Medicare linked database, we identified 2,526 patients with stage IV colorectal cancer diagnosed between 2002 and 2007 who received first-line combination chemotherapy with a fluoropyrimidine and either irinotecan (33%) or oxaliplatin (67%). Thirty-six percent of patients received bevacizumab with first-line therapy. The primary outcome was overall survival. Secondary outcomes were bevacizumab-associated toxicities, including the incidence of stroke, myocardial infarction, and GI perforation.

Results
In the primary cohort inclusive of patients diagnosed between 2002 and 2007, bevacizumab with combination chemotherapy was associated with improved overall survival (adjusted hazard ratio [HR], 0.85; 95% CI, 0.78 to 0.93), although the effect was more modest when restricted to years 2004 to 2007 (HR, 0.93; 95% CI, 0.84 to 1.02). The observed survival advantage of bevacizumab was more apparent with irinotecan-based chemotherapy (HR, 0.80; 95% CI, 0.66 to 0.97) than with oxaliplatin-based chemotherapy (HR, 0.96; 95% CI, 0.86 to 1.07). Combination chemotherapy with bevacizumab, versus combination chemotherapy without bevacizumab, was associated with increased risk of stroke (4.9% *v* 2.5%, respectively; $P < .01$) and GI perforation (2.3% *v* 1.0%, respectively; $P < .01$). Cardiac events and venous thrombosis were not increased with bevacizumab.

Conclusion
The addition of bevacizumab to cytotoxic combination chemotherapy was associated with small improvement in overall survival as well as increased risk of stroke and perforation, but not cardiac events, among Medicare beneficiaries with stage IV colorectal cancer.

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INTRODUCTION

Before 1998, intravenous fluoropyrimidine therapy was the only efficacious option for metastatic colorectal cancer, extending median survival from 6 months without therapy to 1 year.[1] Over the last 13 years, additional drugs have entered the landscape, including two other cytotoxic drugs (irinotecan and oxaliplatin) and targeted monoclonal antibodies (bevacizumab, cetuximab, and panitumumab). First-line randomized controlled trials demonstrated that adding either irinotecan or oxaliplatin to fluoropyrimidines improves median survival by 2 to 4 months.[2-4] In the United States, a weekly bolus regimen of irinotecan, fluorouracil (FU), and leucovorin (IFL) was initially embraced as the standard regimen for chemotherapy-naive patients. Subsequent trials demonstrated that infusional fluoropyrimidine regimens with either oxaliplatin (infusional FU, leucovorin, and oxaliplatin [FOLFOX]) or irinotecan (FU, leucovorin, and irinotecan [FOLFIRI]) are more efficacious[5,6] and less toxic[5] than IFL, leading to a shift from IFL to FOLFOX or FOLFIRI in the mid-2000s.

Bevacizumab, an antibody against the vascular endothelial growth factor, was initially approved by the US Food and Drug Administration (FDA) in 2004 with FU-based chemotherapy as first-line

treatment of metastatic colorectal cancer.[7] The pivotal trial demonstrated that bevacizumab added to IFL improved median survival from 15.6 to 20.3 months ($P < .001$).[8] In a subsequent trial, bevacizumab added to fluoropyrimidine and oxaliplatin improved median overall survival more modestly (21.3 months with bevacizumab *v* 19.9 months without bevacizumab; $P = .08$).[9]

The trials that led the FDA to approve bevacizumab in first-line metastatic colorectal cancer treatment addressed the question of clinical efficacy in patients who met stringent eligibility criteria and were typically younger and healthier than the typical patient with metastatic colorectal cancer. Effectiveness studies examine the impact of treatment in the context of usual care settings, often in populations more diverse by age, race, and health status. To understand the balance of benefits and harms in such a nonclinical trial setting, we used the Surveillance, Epidemiology, and End Results (SEER) -Medicare linked database to compare the effectiveness of cytotoxic chemotherapy treatment with and without bevacizumab in newly diagnosed stage IV colorectal cancer.

PATIENTS AND METHODS

Data Sources

The study cohort was derived from the SEER-Medicare database, which links patient demographic and tumor-specific data collected by SEER cancer registries to the Medicare claims files from the Centers for Medicare and Medicaid Services.[10] Information on patients with new incident cancers was available from 16 cancer registries from 2002 to 2007, covering approximately 26% of the US population. Data on cancer site, extent of disease, histologic findings, date of diagnosis, and initial treatment are available. Date of death was identified from Medicare enrollment records, with follow-up through December 31, 2009, allowing for at least 2 years of follow-up for each patient. Medicare provides health care benefits to 97% of the US population age 65 years or older. Claim histories permit ascertainment of the specific chemotherapy administered. Approximately 94% of SEER patients age 65 years or older have been linked with their Medicare claims.[11]

Cohort Definition

The cohort included all patients age 65 and older who were diagnosed between 2002 and 2007 with colorectal cancer in a SEER area (see Appendix Table A1, online only, for codes used). To assume complete ascertainment of health services, the study sample included all individuals with complete claims, including those with continuous enrollment in Medicare Part A and B and non–health maintenance organization enrollment during the study period.

To be included in the cohort (Fig 1), patients needed to be diagnosed with stage IV colon or rectal cancer and treated with a fluoropyrimidine (either FU or capecitabine) and either oxaliplatin or irinotecan within 6 months of diagnosis. Patients originally diagnosed with early-stage disease who experienced recurrence were not included. The first dose of oxaliplatin or irinotecan must have been billed within 1 month of the first dose of fluoropyrimidine to avoid capturing second-line instead of first-line treatment. Patients classified as receiving bevacizumab received their first dose of bevacizumab within 1 month of the first dose of chemotherapy.

Because alternative cytotoxic regimens may have different efficacy and effectiveness profiles, we scrutinized claims histories to distinguish whether the chemotherapy backbone was IFL (2 to 4 weeks treatment once per week followed by 1- to 2-week break), FOLFIRI (infusional regimen every other week), FOLFOX, or capecitabine plus oxaliplatin. Patients classified as receiving IFL received irinotecan before 2004, or the intervals between irinotecan infusions were 8 days or less on two occasions. Patients classified as receiving FOLFIRI had intervals between irinotecan of 14 days or greater or had charges for an infusion pump (Appendix Table A1).

Bevacizumab was approved by the FDA in February 2004. In our primary analyses (cohort 1), we assume that the care of patients with metastatic colorectal cancer was not sufficiently different outside of the use of bevacizumab from 2002 to 2007. Inclusion of years before FDA approval of bevacizumab addresses concerns for bias by indication because lack of use of bevacizumab after 2004 may be indicative of reasons that may impact survival (although we do adjust by comorbidity in adjusted analyses). However, in sensitivity analyses, we restricted the cohort to patients diagnosed between 2004 and 2007 (cohort 2), when bevacizumab was commercially available and other medications for later-line therapy were available for usage (eg, cetuximab and panitumumab). Furthermore, for patients receiving irinotecan and fluoropyrimidine, there was an increasing shift from IFL to FOLFIRI after 2004, and thus, the cytotoxic chemotherapy regimens FOLFOX and FOLFIRI are more comparable in cohort 2.

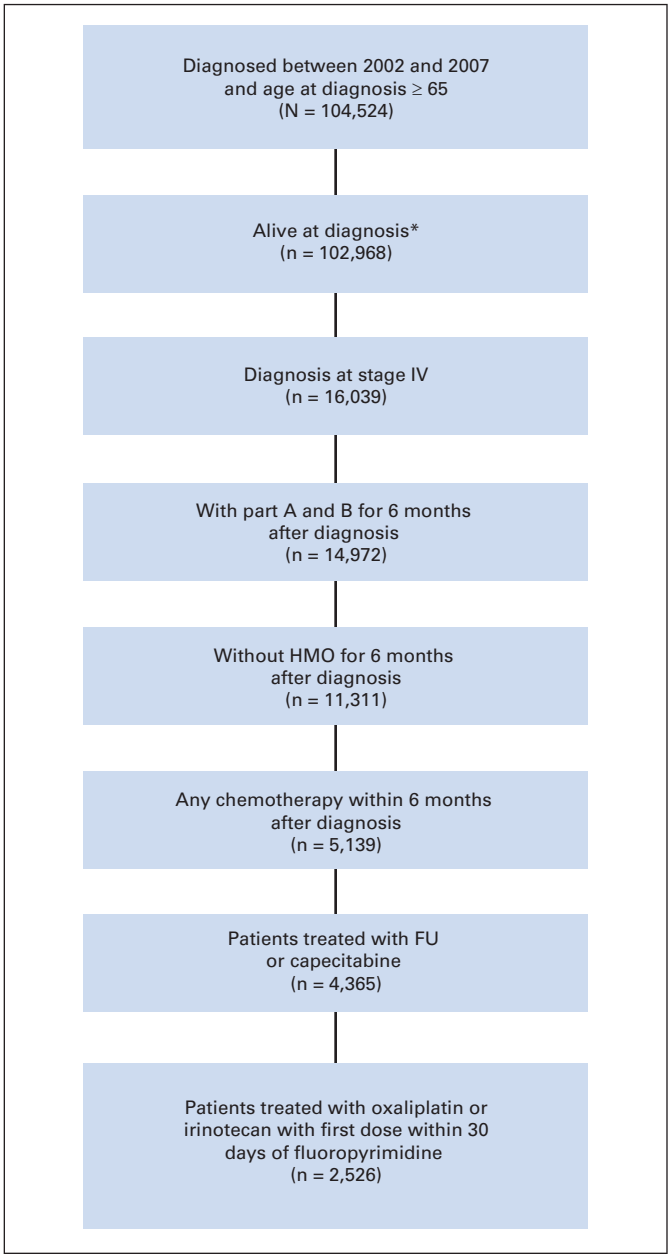

Fig 1. Cohort definition. (*) Small percentage of patients will ultimately be diagnosed after death. FU, fluorouracil; HMO, health maintenance organization.

End Point Definitions

The primary end point was overall survival, which was defined as the interval between date of first dose of chemotherapy and date of death as

Table 1. Baseline Demographics and Clinical Characteristics for Medicare Beneficiaries With Stage IV Colorectal Cancer Diagnosed in a SEER Registry Between 2002 and 2007 Treated With First-Line Combination Chemotherapy

Demographic or Clinical Characteristic	Combination Chemotherapy Without Bevacizumab (n = 1,623) No. of Patients	%	Combination Chemotherapy With Bevacizumab (n = 903) No. of Patients	%
Age, years				
65-69	619	38.1	334	37.0
70-74	461	28.4	271	29.9
75-79	373	23.0	200	22.1
80+	170	10.5	98	10.8
Sex				
Female	769	47.4	418	46.3
Male	854	52.6	485	53.7
Race				
White	1,416	87.2	790	87.5
Black	131	8.1	69	7.6
Other	76	4.7	44	4.9
Comorbidity*				
0	1,098	67.7	606	67.1
1	361	22.2	190	21.1
2+	164	10.1	107	11.8
Marital status				
Married	1,017	62.7	559	61.9
Single	124	7.6	71	7.9
Widowed/divorced	430	26.5	232	25.7
Other	52	3.2	41	4.5
Site of primary				
Colon	1,246	76.8	716	79.3
Rectal	377	23.2	187	20.7
Surgery for primary tumor†				
Yes	1,217	75.0	688	76.2
No	406	25.0	215	23.8
Tumor grade				
Well or moderately differentiated	957	59.0	521	57.7
Poorly differentiated	447	27.5	257	28.5
Unknown	219	13.5	125	13.8
Median income‡				
Top quantile	401	24.7	231	25.6
Second quantile	402	24.8	229	25.4
Third quantile	402	24.8	229	25.4
Bottom quantile	417	25.7	214	23.7
Geographic category for registry				
Northeast	393	24.2	193	21.4
South	302	18.6	193	21.4
Midwest	247	15.2	148	16.4
West	681	42.0	369	40.9
Year of diagnosis				
2002	291	18.0	—	—
2003	316	19.5	—	—
2004	444	27.4	58	6.4
2005	193	11.9	300	33.2
2006	181	11.2	284	31.5
2007	198	12.2	261	28.9
First-line chemotherapy regimen				
Oxaliplatin based	936	57.7	744	82.3
IV FU and oxaliplatin	794		682	
Capecitabine and oxaliplatin	142		62	
Irinotecan based	687	42.3	159	17.7
Bolus (IFL)	548		31	
Infusional (FOLFIRI)§	139		128	
Latter-line therapies received				
Irinotecan first line				
Oxaliplatin	303	44.1	77	48.4
EGFR inhibitor‖	228	33.2	54	34.0
Oxaliplatin first line				
Irinotecan	469	50.1	414	55.6
EGFR inhibitor‖	380	40.5	276	37.1

Abbreviations: EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FU, fluorouracil; IFL, irinotecan, fluorouracil, and leucovorin; IV, intravenous; SEER, Surveillance, Epidemiology, and End Results.

*The Deyo-Charlson-Klabunde comorbidity index, derived from inpatient and outpatient Medicare claims for the period extending from 13 months before stage IV colorectal cancer diagnosis to 1 month before diagnosis.

†Based on Medicare claims filing.

‡Patient's zip code of residence served as a proxy of socioeconomic status.

§Infusional includes IV FU or capecitabine.

‖Cetuximab or panitumumab.

reported to Medicare or December 31, 2009, whichever occurred first. Secondary end points were inpatient and outpatient events associated with bevacizumab, including cardiac toxicity, stroke, venous thrombosis, and GI perforation (Appendix Table A1).[8]

Patient Characteristics Associated With Treatment and Outcomes

Using the SEER-Medicare files, we evaluated clinical characteristics, demographic data, and the Deyo-Charlson-Klabunde comorbidity index.[12] The comorbidity index includes myocardial infarction, congestive heart failure, peripheral vascular disease, and cardiovascular and cerebrovascular disease, thereby capturing many of the absolute or relative contraindications to bevacizumab. All available inpatient and outpatient Medicare claims were examined for the period between 13 months and 1 month before the diagnosis of stage IV colorectal cancer, and patients were scored by maximal comorbidity observed (0, 1, or 2+).

Statistical Considerations

Overall survival was examined using the Kaplan-Meier method[13] and Cox proportional hazards regression for both the 2002 to 2007 and 2004 to 2007 cohorts.[14] Multivariable modeling was used to adjust for potential confounders and propensity scores[15] to further examine for potential treatment selection bias.

Toxicity analyses were performed using logistic regression modeling, adjusting for potential confounders as well as propensity scores.[15] All analyses used SAS version 9.1 (SAS Institute, Cary, NC). All *P* values are two-sided.

RESULTS

Patient Demographics

We identified 2,526 patients diagnosed with stage IV colorectal cancer between 2002 and 2007 and treated with fluoropyrimidine therapy and either oxaliplatin or irinotecan within the first 6 months of diagnosis (Table 1). Of these, 903 patients (36%) received bevacizumab within 4 weeks of initiation of chemotherapy. Patients receiving bevacizumab were more likely to receive oxaliplatin (82.3%) compared with patients not receiving bevacizumab (57.7%). Otherwise, the distribution of tumor characteristics and patient demographics was similar between patients receiving and patients not receiving first-line bevacizumab (Table 1).

Overall Survival With or Without Bevacizumab

The addition of bevacizumab to fluoropyrimidine and either oxaliplatin or irinotecan led to a statistically significant improvement in overall survival (Table 2) with an unadjusted hazard ratio (HR) of 0.87 (95% CI, 0.80 to 0.95; $P = .003$). Median overall survival was 19.0 months with bevacizumab and 15.9 months without bevacizumab (Fig 2A). The adjusted HR was 0.85 (95% CI, 0.78 to 0.93). Similar associations were observed adding propensity scores into the model. In the subset of patients diagnosed between 2004 and 2007, the adjusted HR was 0.93 (95% CI, 0.84 to 1.02).

For patients who received oxaliplatin and fluoropyrimidine (Fig 2B), there was no apparent benefit of bevacizumab on survival (adjusted HR, 0.96; 95% CI, 0.86 to 1.07). In contrast, bevacizumab usage was associated with an improved overall survival for patients treated with irinotecan and fluoropyrimidine ($P = .03$; Fig 2C). The adjusted HRs comparing bevacizumab to no bevacizumab with irinotecan were 0.80 (95% CI, 0.66 to 0.97) in patients diagnosed between 2002 and 2007 and 0.86 (95% CI, 0.68 to 1.08) in patients diagnosed between 2004 and 2007. Bevacizumab-treated patients receiving irinotecan, compared with patients not treated with bevacizumab, had slightly greater use of second-line oxaliplatin (48.4% *v* 41.5%, respectively) and epidermal growth factor receptor inhibitors (34.0% *v* 30.9%, respectively).

We explored the association between bevacizumab and overall survival according to whether irinotecan was administered as a bolus (IFL) or infusion (FOLFIRI; Fig 2D). Median overall survival was 18.1 months for IFL plus bevacizumab (n = 31) compared with 13.0 months with IFL alone (n = 548), with an adjusted HR of 0.72 (95% CI, 0.48 to 1.09). Median overall survival was 18.1 months for FOLFIRI with bevacizumab (n = 128) compared with 13.3 months with FOLFIRI only (n = 139), with an adjusted HR of 0.88 (95 CI, 0.67 to 1.15).

Sensitivity Analyses

We defined first-line use of bevacizumab as receipt within 1 month of the first dose of cytotoxic chemotherapy. We tested an alternative definition of bevacizumab within 6 months of start of therapy; 396 additional patients received bevacizumab between 1 and 6 months of first dose of chemotherapy. With this definition, the adjusted HR for bevacizumab effectiveness was 0.87 (95% CI, 0.80 to 0.95). In extending bevacizumab usage to within 6 months, the improved survival observed with bevacizumab remained limited to irinotecan-based chemotherapy (data not shown).

Bevacizumab-Associated Toxicities

We examined toxicities encountered within the first 2 and 6 months of initiation of chemotherapy (Table 3). Bevacizumab was associated with a higher rate of stroke (4.9% *v* 2.5% without bevacizumab) within the first 6 months of therapy. In contrast and contrary to our expectation, the overall rate of cardiac events was less with bevacizumab than without bevacizumab (11.5 *v* 14.5%, respectively). We considered whether this discrepancy was related to bias by indication, whereby patients not receiving bevacizumab were more likely to

Table 2. HRs for Overall Survival Comparing First-Line Combination Chemotherapy With Bevacizumab to First-Line Combination Chemotherapy Without Bevacizumab by Treatment Regimen and Year of Diagnosis

	2002-2007					2004-2007				
Measure	Any Combination Chemotherapy	Irinotecan-Based Therapy	Infusional FU* + Irinotecan	Bolus FU + Irinotecan	Oxaliplatin-Based Therapy	Any Combination Chemotherapy	Irinotecan-Based Therapy	Infusional FU* + Irinotecan	Bolus FU + Irinotecan	Oxaliplatin-Based Therapy
Received bevacizumab, No. of patients										
Yes	903	159	128	31	744	903	159	128	31	744
No	1,623	687	139	548	936	1,016	193	123	70	823
Overall survival										
Unadjusted HR	0.87	0.81	0.83	0.82	0.97	0.93	0.85	0.79	0.91	0.96
95% CI	0.80 to 0.95	0.67 to 0.98	0.64 to 1.08	0.55 to 1.21	0.87 to 1.08	0.85 to 1.03	0.68 to 1.06	0.60 to 1.02	0.57 to 1.44	0.86 to 1.07
Adjusted HR by multivariate modeling†	0.85	0.80	0.88	0.72	0.96	0.93	0.86	0.88	0.83	0.95
95% CI	0.78 to 0.93	0.66 to 0.97	0.67 to 1.15	0.48 to 1.09	0.86 to 1.07	0.84 to 1.02	0.68 to 1.08	0.67 to 1.16	0.50 to 1.40	0.85 to 1.06
Adjusted HR by propensity scores†	0.85	0.80	0.83	0.74	0.96	0.93	0.83	0.85	0.90	0.95
95% CI	0.78 to 0.94	0.66 to 0.96	0.64 to 1.09	0.49 to 1.13	0.86 to 1.07	0.84 to 1.03	0.65 to 1.05	0.65 to 1.13	0.51 to 1.57	0.85 to 1.06

Abbreviations: FU, fluorouracil; HR, hazard ratio.
*Infusional FU or capecitabine.
†Adjusting covariates include age, sex, race, comorbidity, marital status, primary tumor site, tumor grade, history of primary tumor surgery, median household income, and regimen.

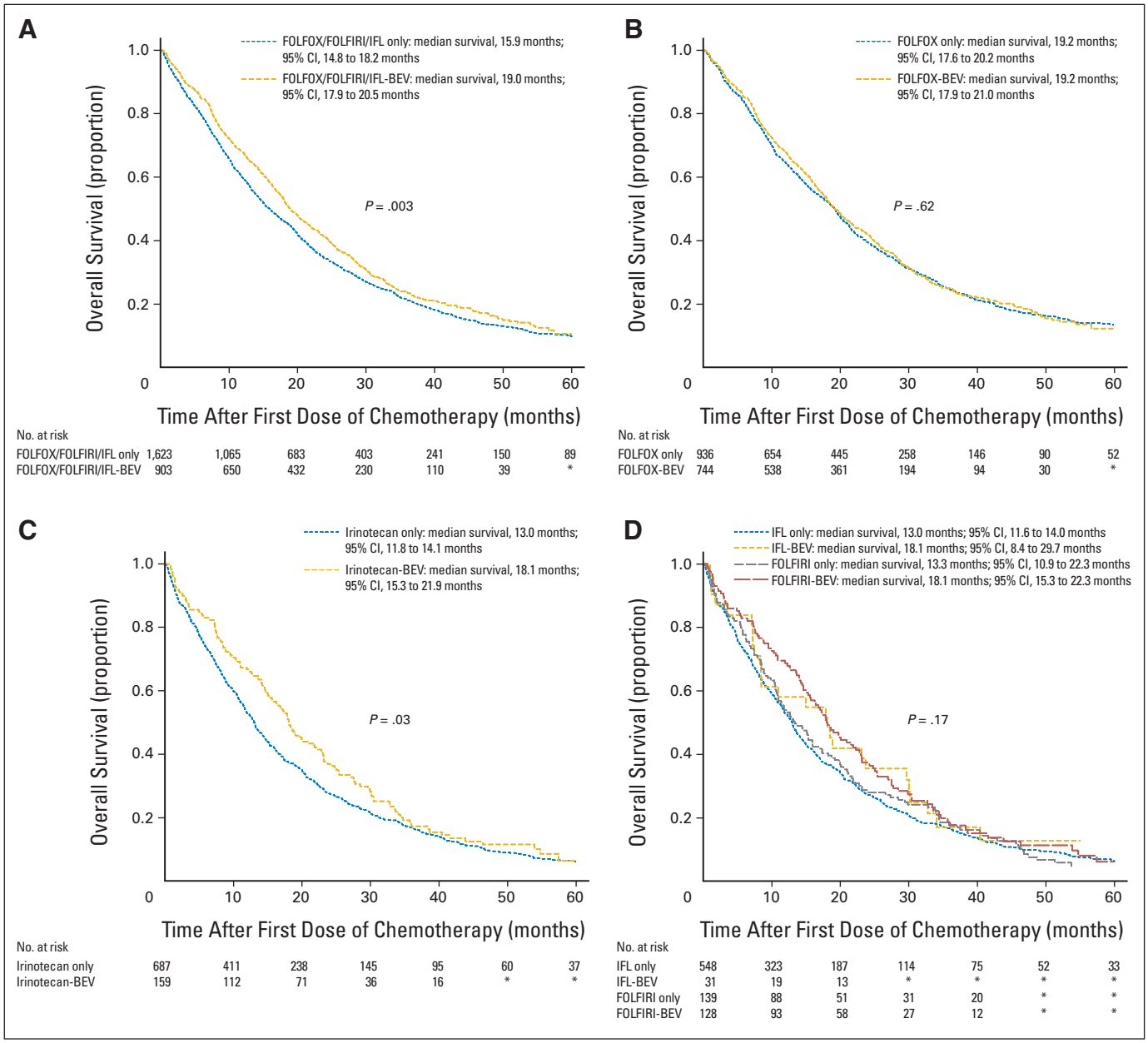

Fig 2. Kaplan-Meier curves comparing overall survival for combination chemotherapy with or without bevacizumab (BEV): (A) either oxaliplatin or irinotecan with fluoropyrimidine (n = 1,484); (B) oxaliplatin with fluoropyrimidine (n = 781); (C) irinotecan with fluoropyrimidine (n = 703); and (D) subsets of irinotecan by fluoropyrimidine delivery. (*) n < 11; masked to protect patient confidentiality. FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; IFL, irinotecan, fluorouracil, and leucovorin.

have recent cardiac history (defined as within 12 months of initial treatment). Among 166 patients with a history of an arterial thrombotic event, 39% received bevacizumab. In those patients, there was no difference in the rate of cardiac events associated with bevacizumab within 6 months of first treatment (5.4% *v* 5.5% without bevacizumab). However, patients who had not had a prior arterial event had a lower rate of cardiac events with bevacizumab versus with bevacizumab (6.1% *v* 9.0%, respectively). Adverse events within the first 12 months of therapy were similar to those within the first 6 months (data not shown).

Rates of venous thrombosis were not appreciably different with or without bevacizumab (20.4% *v* 21.1%, respectively). The rates of GI tract perforation were significantly greater with versus without bevacizumab (2.3% *v* 1.0%, respectively).

We explored rates of toxicities based on whether the cytotoxic chemotherapy backbone was oxaliplatin or irinotecan. Rates of cardiac events, strokes, deep venous thrombosis, and GI perforations were comparable by chemotherapy (data not shown).

Mortality within 60 days of start of chemotherapy is a reported end point in clinical trials.[16] In this cohort, 4.9% of patients receiving bevacizumab in first-line therapy died of any cause compared with 7.9% of patients not receiving bevacizumab ($P < .004$) within the first 60 days of therapy. This finding was consistent by number of comorbidities associated with the patient. Sixty-day mortality rates

Table 3. Bevacizumab-Associated Toxicities Comparing Treatment With Bevacizumab in Years 2004 to 2007 (n = 903) to Treatment Without Bevacizumab in Years 2002 to 2007 (n = 1,623)

Toxicity	With Bevacizumab		Without Bevacizumab		Difference (%)	95% CI (%)	*P*	Adjusted by Multivariate Model		Adjusted by Propensity Scores	
	No. of Patients	%	No. of Patients	%				OR	95% CI	OR	95% CI
Within 60 days of first chemotherapy treatment											
Cardiac, all	55	6.1	128	7.9	−1.8	−3.8 to 0.2	.10	0.69	0.49 to 0.96	0.68	0.48 to 0.95
No history of cardiac event or stroke within 12 months of diagnosis	25	2.8	73	4.5	−1.7	−3.0 to −0.3	.03	0.58	0.37 to 0.93	0.57	0.36 to 0.92
History of cardiac event or stroke within 12 months of diagnosis	30	3.3	55	3.4	−0.1	−1.5 to 1.4	.93	0.85	0.52 to 1.37	0.84	0.52 to 1.36
Stroke, all	13	1.4	16	1.0	0.4	−0.5 to 1.4	.30	1.44*	0.68 to 3.03	1.44*	0.69 to 3.04
No history of cardiac event or stroke within 12 months of diagnosis	†		†		0.2	−0.5 to 0.9	.50	1.44	0.53 to 3.90	1.51	0.55 to 4.12
History of cardiac event or stroke within 12 months of diagnosis	†		†		0.2	−0.4 to 0.9	.56	1.53	0.50 to 4.69	1.50	0.49 to 4.64
Deep venous thrombosis or pulmonary embolism	98	10.9	194	12.0	−1.1	−3.7 to 1.5	.41	0.89	0.68 to 1.15	0.88	0.68 to 1.15
GI perforation (n = 18)	†		†		0.6	−0.2 to 1.4	.08	2.15	0.83 to 5.54	2.17	0.84 to 5.65
60-day all-cause mortality (n = 172)	44	4.9	128	7.9	3.0	1.1 to 4.9	< .01	0.58	0.41 to 0.84	0.59	0.41 to 0.84
Within 6 months of first chemotherapy treatment											
Cardiac, all	104	11.5	236	14.5	−3.0	−5.7 to 0.3	.03	0.71	0.55 to 0.92	0.70	0.54 to 0.91
No history of cardiac event or stroke within 12 months of diagnosis	55	6.1	146	9.0	−2.9	−5.0 to −0.8	.01	0.64	0.46 to 0.89	0.64	0.46 to 0.89
History of cardiac event or stroke within 12 months of diagnosis	49	5.4	90	5.5	−0.1	−2.0 to 1.7	.90	0.87	0.59 to 1.28	0.85	0.58 to 1.26
Stroke, all	44	4.9	41	2.5	2.4	0.8 to 3.9	< .01	2.01	1.29 to 3.11	2.00	1.29 to 3.10
No history of cardiac event or stroke within 12 months of diagnosis	24	2.7	25	1.5	1.1	−0.1 to 2.3	.05	1.76	1.00 to 3.12	1.75	0.99 to 3.10
History of cardiac event or stroke within 12 months of diagnosis	20	2.2	16	1.0	1.2	0.2 to 2.3	.01	2.22*	1.12 to 4.39	2.21*	1.11 to 4.38
Deep venous thrombosis or pulmonary embolism	184	20.4	342	21.1	−0.7	−4.0 to 2.6	.68	0.96	0.78 to 1.18	0.96	0.79 to 1.18
GI perforation (n = 18)	21	2.3	16	1.0	1.3	0.3 to 2.4	< .01	2.36	1.21 to 4.60	2.43	1.24 to 4.75

Abbreviation: OR, odds ratio.
*Adjusting covariates include age, sex, comorbidity, primary tumor site history of primary tumor surgery, and median household income.
†n < 11; masked to protect patient confidentiality.

were 4%, 7%, and 6% in patients receiving bevacizumab with comorbidity scores of 0, 1, or 2+, respectively, and 7%, 9%, and 10% in patients not receiving bevacizumab with comorbidity scores of 0, 1, or 2+, respectively (*P* for interaction = .75). Similarly, there was no interaction between 60-day mortality and surgery for primary tumor (data not shown).

DISCUSSION

Randomized clinical trials have demonstrated that bevacizumab improves overall and/or progression-free survival when added to first-line cytotoxic chemotherapy in metastatic colorectal cancer.[8,9,17] Using the SEER-Medicare linked database, we evaluated the effectiveness of bevacizumab with combination chemotherapy in the Medicare population. The addition of bevacizumab to fluoropyrimidine and either oxaliplatin or irinotecan led to a statistically significant improvement in overall survival, although the benefit seemed limited to patients receiving irinotecan-based chemotherapy regimens and not evident in patients treated with oxaliplatin-based chemotherapy. The addition of bevacizumab to cytotoxic chemotherapy increased the rates of strokes and GI perforations but not cardiac events.

Bevacizumab was initially tested in colorectal cancer in a small, randomized phase II trial with FU and leucovorin.[18] The results led to a phase III trial of IFL with or without bevacizumab that demonstrated a significant improvement in median overall survival from 15.6 to 20.3 months (HR, 0.66; $P < .001$).[8] By the time of FDA approval of bevacizumab, IFL was no longer the preferred first-line regimen for colorectal cancer. There was an increasing shift from IFL to FOLFOX based on results from North Central Cancer Treatment Group trial 9741, showing a survival advantage with FOLFOX compared with IFL

(HR, 0.74; $P = .0014$).[6] IFL was also supplanted in practice by FOLFIRI. Likely because of these shifts in cytotoxic therapy backbone, the FDA approved bevacizumab in combination with intravenous FU-based chemotherapy, not restricting usage with only IFL but enabling usage of bevacizumab with FU alone, IFL, FOLFIRI, or FOLFOX. Perhaps because bevacizumab is a biologic agent, and not a cytotoxic agent, both oncologists and the FDA were more willing to combine it with an infusional FU and irinotecan regimen or oxaliplatin-based therapy, initially in the absence of efficacy data. For many oncologists, FOLFOX and bevacizumab became the regimen of choice in the United States. Two nonrandomized, observational studies of patients receiving bevacizumab with combination chemotherapy (including IFL, FOLFOX, FOLFIRI, or capecitabine and oxaliplatin) confirmed progression-free survival of 9.6 to 10.8 months,[19,20] with one cohort reporting comparable progression-free survival (although reduced overall survival) in elderly patients.[19] However, these cohorts did not collect data from patients not receiving bevacizumab to serve as a comparison. Furthermore, most subsequent phase III trials of first-line therapy incorporate bevacizumab in both arms of the study.[7,21,22]

The goal of effectiveness research is to understand the outcomes of treatments as they are adopted by real-world practitioners who face everyday treatment decisions in the face of multiple studies and patients whose attributes do not exactly correspond to the clinical trial eligibility criteria. However, data from a phase III trial of oxaliplatin-based therapy with or without bevacizumab[9] and our effectiveness results suggest that the magnitude of benefit combining bevacizumab with oxaliplatin is more modest than originally observed for IFL and bevacizumab. This difference by chemotherapy backbone may suggest a differential benefit when bevacizumab is added to irinotecan compared with oxaliplatin, although such a biologic interaction has not been reported.

We anticipated that the rates of major toxicities such as stroke, perforation, and cardiovascular events would have been substantially greater in the Medicare population than those encountered in the efficacy studies. Notably, toxicities detected in our effectiveness cohort are only marginally higher for bevacizumab-treated patients and are similar to the rates reported in clinical trials. Administrative claims data are not optimized for identification of certain bevacizumab-associated adverse effects such as hypertension, proteinuria, and delayed wound healing. However, major toxicities such as stroke, perforation, and myocardial infarction are well captured in billing claims. Bevacizumab did not result in a substantially higher rate of myocardial infarction or venous thrombosis in this cohort, although there was a modestly higher rate of strokes and GI perforations.

The advantage of using the SEER-Medicare linked database is that the choice of chemotherapy regimens is not limited to the stringent treatment program required in clinical trials and analysis by chemotherapy type is possible. Such analyses also capture the outcomes of real-world usage of these medications, outside of protocol-prescribed dose modifications and treatment holds.

Several limitations of this analysis must be noted. The potential for inaccurate coding exists for any claims-based analysis, clinical information available from billing records is not as detailed as from chart reviews or clinical trials, and the details of dose modification could not be captured.[11] Our results may not generalize to the non-Medicare population or the approximately 16% of Medicare beneficiaries who receive care in a health maintenance organization setting, where patterns of care may be different.[23] However, because two thirds of patients with colorectal cancer are over age 65 years and Medicare is the primary insurer for the vast majority, our study represents the care received by typical US patients with colorectal cancer. Because identification of recurrent cancer is challenging using administrative data, we restricted our cohort to patients with stage IV colorectal cancer. Most clinical trials do not identify substantial differences in prognosis for patients with stage IV disease and patients with recurrent metastatic disease. However, some caution is nonetheless warranted because our results may not generalize to patients with recurrent metastatic disease. In the context of an observational cohort study, we cannot be certain that the survival differences we observed are a result of bevacizumab or alternatively a result of baseline differences in patient attributes. Our baseline data do not demonstrate appreciable differences in baseline characteristics, and we used propensity score modeling to adjust for potential biases. Nonetheless, 60-day mortality is greater in patients not receiving bevacizumab. This difference may be a result of chance or an actual early benefit of therapy that includes bevacizumab. Alternatively, patients receiving bevacizumab may be different from patients not receiving bevacizumab, and this difference may be associated with early mortality risk.

In conclusion, the addition of bevacizumab to first-line therapy for metastatic colorectal cancer significantly improved overall survival in a cohort derived from the linked SEER-Medicare database. The data from this analysis suggest the benefit is derived from irinotecan-based regimens, with marginal benefit in oxaliplatin-treated patients. Furthermore, the benefit of bevacizumab was more attenuated in the latter years when there was an increasing shift away from bolus to infusional fluoropyrimidine regimens, increased availability of latter-line epidermal growth factor inhibitors, and more aggressive surgical management of limited stage IV disease. An ideal trial to answer the question of whether bevacizumab benefit is truly limited to irinotecan-based regimens would be a 2×2 randomization between FOLFOX and FOLFIRI plus or minus bevacizumab. However, because multiple prior FOLFOX versus FOLFIRI trials have been reported and suggest noninferiority between the two regimens (albeit none have included bevacizumab),[24,25] enthusiasm for such a trial would be low. In summary, the routine use of bevacizumab in combination with cytotoxic chemotherapy for Medicare beneficiaries with stage IV colorectal cancer is associated with a modest survival advantage and a modest excess risk of harms from perforation and stroke. On balance, elderly patients with colorectal cancer can be counseled that including bevacizumab in first-line therapy regimens for metastatic colorectal cancer seems to be no more than marginally effective.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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