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Bevacizumab use and risk of cardiovascular adverse events among elderly patients with colorectal cancer receiving chemotherapy: a population-based study

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Background: Cardiovascular risk attributable to bevacizumab (Avastin®, BEV) for treatment of metastatic colorectal cancer (CRC) remains unclear. We conducted a population-based cohort study to assess the safety of BEV use among patients aged ≥65.

Patients and methods: We identified CRC patients diagnosed from 2005 to 2007 who received chemotherapy and were followed until 31 December 2009. Outcomes were 3-year risk of arterial thromboembolic events (ATEs), cardiomyopathy or congestive heart failure (CM/CHF), and cardiac death (CD) after chemotherapy initiation. We fitted Cox-proportional hazards (PHs) models with inverse-probability-of-treatment-weights and calculated hazard ratios (HRs) for the risk of adverse events.

Results: We identified 6803 CRC patients (median age: 73 years). Those with cardiac comorbidity were less likely to receive BEV ($P < 0.0001$). BEV is associated with an elevated risk of ATEs (HR = 1.82, 95% CI = 1.20–2.76, $P < 0.001$; rate difference: 3.5 additional cases/1000 person-years). We observed no association between BEV and CD or CM/CHF.

Conclusions: In general practice, the cardiovascular risk of BEV in elderly CRC is modest. The observed ATEs risk is lower than reported in clinical trials, which may be due to careful patient selection. Our findings may facilitate clinical decision-making of BEV use in elderly patients.

Key words: adverse events, arterial thromboembolic events, bevacizumab, cardiac death, congestive heart failure

introduction

Colorectal cancer (CRC) accounts for over 600 000 annual deaths worldwide and more than 1.23 million new cases are reported every year [1]. In the United States, ∼30% of newly diagnosed CRC patients are metastatic and two-thirds of these patients are older than 65 [2]. In the past decade, several novel efficacious targeted molecular therapies have been introduced to treat metastatic CRC [3–5]. One such therapy is bevacizumab (Avastin®, Genentech/Roche), a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor A (VEGF-A). In 2004, bevacizumab (BEV) became the first US Food and Drug Administration (FDA)-approved anti-angiogenesis agent for metastatic CRC [4]. By binding specifically to VEGF-A, BEV prevents the proliferation of endothelial cells and formation of new blood cells, thus, inhibiting tumor growth and metastasis.

The benefits of BEV treatment in metastatic CRC patients have been confirmed in randomized, control studies. A study of 813 previously untreated metastatic CRC patients found that BEV added to a combined therapy of irinotecan, 5-FU, and leucovorin significantly prolonged overall survival [20.3 versus 15.6 months, hazard ratio (HR) = 0.66, $P < 0.01$] and disease-free survival (10.6 versus 6.2 months, HR = 0.54, $P < 0.001$) over combined therapy alone [4]. A study of 829 refractory metastatic CRC patients previously treated with a combined therapy of oxaliplatin, 5-FU and leucovorin with and without BEV also found that BEV prolonged overall median survival (12.9 versus 10.8 month, HR = 0.75, $P < 0.001$) [6]. A meta-analysis of 3385 metastatic CRC patients from six trials found that patients who received BEV with chemotherapy experienced improved overall survival (HR = 0.80, $P < 0.001$) and progression-free survival (HR = 0.62, $P < 0.001$) when compared with patients receiving chemotherapy alone [7].

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While BEV efficacy has been demonstrated, the safety of BEV use in older populations remains questionable. BEV is associated with an increased risk of high-grade hypertension, bleeding, venous thromboembolic events, decreased wound healing, gastrointestinal perforation, and proteinuria [7]. However, the increased risk of arterial thromboembolic events (ATEs) remains inconclusive with a 0%–5% increase for patients over 65 years of age with a history of ATEs [8–10]. Although explicit association between BEV use and the risk of cardiomyopathy or congestive heart failure (CM/CHF) and cardiac death have not been reported among CRC patients enrolled in clinical trials, cardiovascular events after BEV use have been commonly reported in the US FDA's Adverse Event Reporting System [11]. It is biologically feasible to suspect cardiovascular side-effects with BEV use. Studies have shown that the anti-VEGF effect of BEV may increase hypertension through reduced production of nitric oxide in the walls of arterioles and through altering receptors on the renin–angiotensin–aldosterone pathway [12, 13]. Additionally, BEV may increase the risk of congestive heart failure in patients with metastatic breast cancer [14].

Our study examines whether BEV use increases the risks of ATEs, CM/CHF, and cardiac death among CRC patients over 65 years of age who have received chemotherapy. Most randomized studies have enrolled relatively few patients in this age group [6, 8, 9, 15]. Some studies reported serious side-effects from BEV use in patients older than 65, but the findings were inconsistent [15–18]. Inconclusive reports on the cardiovascular risk associated with BEV may affect clinical decision-making in prescribing BEV to metastatic CRC patients over 65, which account for two-thirds of metastatic CRC patients; cardiovascular comorbidity is more prevalent among this age group. Therefore, we conducted a retrospective cohort study of advanced CRC patients aged ≥65 to determine the safety of BEV use in general clinical practice.

patients and methods

design and data source

We identified eligible patients from the Surveillance, Epidemiology, and End Results (SEER) cancer registries data linked to Medicare claims data. Details about the SEER–Medicare linked database are described elsewhere [19]. Briefly, the SEER registries, funded by the US National Cancer Institute, are population-based cancer registries that collect cancer incidence data in ∼26% of the US population. From the SEER registries, we obtained information on sociodemographic characteristics, year of diagnosis, clinical stage, geographic region, and initial cancer-directed radiation and surgery for all incident CRC patients. The registries link their cases to state death certificates to determine the cause of death of the SEER participants. Persons in the SEER data have been matched to Medicare data where patient Medicare claims have been extracted.

Four types of Medicare claims were used in this study to identify comorbidities, adverse events, and chemotherapy utilization: inpatient hospital records, physician claims, outpatient bills from institutional providers, and Durable Medical Equipment files.

patient population

Our cohort included individuals aged ≥65 diagnosed with CRC as their first or only primary cancer from 1 January 2005 to 31 December 2007 and received chemotherapy any time from diagnosis through 2009. We refined the cohort to include only patients with newly diagnosed metastatic disease (American Joint Committee on Cancer Stage IV) or patients who were initially diagnosed with localized/regional disease (stages II and III) which later progressed to metastatic disease defined as receiving more than one standard chemotherapy agent (5-FU, oxaliplatin, irinotecan) after 8 months of initial diagnosis. We excluded patients who either (i) had prior cancer history other than CRC ($n = 2181$) to avoid bias due to effects of any prior chemotherapy for other malignancies; (ii) were not enrolled in both Medicare A and B or were enrolled in Health Maintenance Organizations ($n = 1390$) to minimize misclassification of treatment information and outcomes or (iv) died within 1 month of diagnosis ($n = 14$). These exclusions resulted in a cohort of 6803. In our assessment for the incident risk of ATEs and CM/CHF, only patients with no history of ATE ($n = 6370$) or CH/CHF ($n = 6195$), respectively, were included in order to avoid misclassification of a new event with follow-up for a prior condition.

treatment characteristics

We extracted chemotherapy administration dates using Healthcare Common Procedure Coding System (HCPCS) code for each standard regimen cycle used to treat CRC including BEV, 5-FU, capecitabine, oxaliplatin, irinotecan, and epidermal growth factor receptor inhibitors. We ascertained usage of radiation therapy using the union of SEER data and Medicare claims starting 3 months before chemotherapy using ICD-9 diagnoses along with the procedure, HCPCS, and revenue center codes [20]. Information on cancer-directed primary surgery was obtained from SEER registry. Medicare-derived coding for capturing outcomes and chemotherapy use is summarized in supplementary material Appendix S1, available at *Annals of Oncology* online.

outcomes assessments

We used pre-specified ICD-9 codes to capture the first occurrence of cardiovascular event after chemotherapy initiation (time zero) through the end of follow-up (31 December 2009). Cardiovascular events included ATEs (acute myocardial infarction; arterial embolism and thrombosis; transient ischemic attack; angina), CM/CHF, and cardiac death. Adverse events met any of the following three criteria: one primary diagnosis from inpatient claims; two outpatient records at least 30 days apart or one secondary diagnosis from inpatient claims plus one outpatient diagnosis. We applied these criteria to maximize the inclusion of incident adverse events and minimize the possibility of 'rule-out' diagnoses. We captured cardiac deaths from the underlying cause of death reported by the SEER Program registries using ICD-10 codes (I-059 to 959).

covariates measurement

Using ICD-9 codes from inpatient and physician claims, we identified cardiovascular comorbidity, including ATEs, CM/CHF, and general cardiac conditions (hypertension, arrhythmic disorders, cardiomyopathic disorders, pericardial disorder, aortic wall disorders, and cardiopulmonary arrest) within 1 year before chemotherapy initiation. A modified Charlson index was calculated as a measure of comorbid conditions [21]. Given our focus on ATEs and CM/CHF events, we excluded myocardial infarction and congestive heart failure from the Charlson index calculation to avoid redundant adjustment.

We measured the socioeconomic status using the median household income and percentage of adults with less than a high school education at the census tract level. These variables were obtained from the US Bureau of the Census and are included in the distributed SEER-Medicare database [22, 23].

statistical analysis

We first computed summary statistics to describe patient characteristics. We then applied chi-square tests to compare sociodemographics and clinical characteristics according to BEV use in our study cohort.

Because of the nature of observational study design, we carried out propensity score (PS) analysis to reduce selection bias in assessing the risk of CM/CHF with BEV [24, 25]. We first fit a multiple logistic regression model to estimate the probability of receiving BEV. Independent variables in this logistic regression model included age at chemotherapy initiation, sex, race/ethnicity, geographic region, stage at initial diagnosis, comorbidity, prior history of cardiovascular conditions, and group-level socioeconomic status. We plotted the PS distribution according to BEV use to confirm sufficient overlap of the PS distribution between the two groups. We evaluated the performance of the PS model by checking whether the standardized differences in proportions (for binary variables) or in means (for continuous variables) between groups were <10% after PS adjustment [25].

We then fit the Cox-proportional hazards (PHs) models with inverse probability of treatment weights to estimate associations between BEV use and the risk of each adverse outcome [26, 27]. In each outcome model, follow-up time starts at chemotherapy initiation and extends to the earliest of the following: occurrence of adverse cardiac event, death or end of the study date (31 December 2009). In our outcome models, we adjusted for patient sociodemographics, history of cardiac conditions, and treatments given after diagnosis such as radiation therapy, surgery, and specific chemotherapy agents. The chemotherapy agents were treated as time-dependent covariates in the Cox-PHs models.

To assess whether different subpopulations have different risks associated with BEV, we conducted subgroup analysis by age of chemotherapy initiation (> or < 75 years old (median age); younger or and older than 80 years old), sex, history of cardiac conditions, and recipient of radiation, surgery and specific chemotherapy agents. As a sensitivity analysis, we carried out conventional Cox-PH models without PS adjustment. Data analyses were carried out using SAS 9.2 (Cary, NC) and STATA 10.1 (College Station, TX). All P values were two-sided, and $P < 0.05$ was considered statistically significant.

results

population characteristics

The cohort included 6803 incident CRC patients aged ≥65 who received chemotherapy between 2005 and 2009. The median age of CRC patients in both the BEV and non-BEV groups was 73 years (Table 1). Of these patients, 41% received BEV during the follow-up period. BEV-treated patients were more likely to have stage IV disease as their initial diagnosis than non-BEV-treated patients. Around 50% of BEV treatment was prescribed within 16 days of chemotherapy initiation and the median length of BEV use was ∼5.6 months. CRC patients receiving BEV treatment had a significantly lower percentage of pre-treatment cardiac comorbidity and ATEs history compared with those not receiving BEV treatment ($P < 0.0001$). After adjusting for the PS weights, the distribution of these two variables and other covariates was balanced ($P > 0.05$) between the BEV-treated and non-BEV-treated groups.

risk of ATEs, CHF and cardiac death

There was an unadjusted 2.6% 3-year risk of incident ATEs in our cohort (165 cases out of 6370 CRC patients without any history of ATEs). The absolute incidence rates of ATEs were 15.9 and 12.4 per 1000 person-years follow-up among metastatic CRC patients with and without BEV use, respectively. We observed an increased risk of ATEs among CRC patients receiving chemotherapy and BEV (adjusted HR = 1.82, 95% CI = 1.20, 2.76) (Table 2). When we divided the risk time window into two periods, during BEV treatment and after BEV treatment completion, we found that the risk of ATEs did not differ between these two periods. We did not observe any significant sub-group effects for the risk of ATEs.

We observed a 2.9% 3-year crude risk of incident CM/CHF events (179 cases out of 6195 CRC patients without prior

Table 1. Distribution of sociodemographic and clinical characteristics among colorectal cancer patients ($n = 6803$) aged ≥65 diagnosed from 2005–2007 receiving chemotherapy with versus without bevacizumab (BEV) for metastatic or recurrent disease

Population characteristics	Total % ($N = 6803$)	No Bev % ($N = 4016$)	Bev % ($N = 2787$)
Age at first chemotherapy (years)			
65–69	29	29	30
70–74	27	26	27
75–80	24	24	24
80+	20	20	19
Sex			
Female	50	50	49
Male	50	50	51
Race			
White	84	83	84
Black	8	8	8
Other	8	9	8
AJCC stage at diagnosis**			
2	18	23	12
3	44	54	28
4	38	23	60
Revised comorbidity index[a]			
None	60	59	61
1	28	29	26
2+	12	12	13
History of medical conditions[b]			
Cardiac disease**			
Yes	60	62	56
No	40	38	44
Arterial thromboembolic events (ATEs)*			
Yes	5	6	4
No	95	94	96
Congestive heart failure/cardiomyopathy (CHF/CM)			
Yes	12	13	11
No	88	87	89

[a]Charlson's Index with exclusion of myocardial infarction and congestive heart failure.

[b]History of general cardiac conditions includes the following diseases: hypertension, arrhythmic disorders, cardiomyopathic disorders, pericardial disorder, aortic wall disorders, and cardiopulmonary arrest.

* and ** indicated a variable with an unadjusted chi-square P value smaller than 0.001 and 0.0001, respectively.

Table 2. Risk of arterial thromboembolic events (ATEs) up to 36 months of follow-up among colorectal cancer patients diagnosed during 2005–2007, no ATE history, and receiving chemotherapy with or without bevacizumab for newly diagnosed or recurrent disease

	Event no.[a]	Event rate (per 1000 person-years)	Hazard ratio (HR, 95% CI)[b]
BEV use	56	15.90	1.82 (1.20, 2.76)*
Non-BEV	109	12.38	1.0

[a]The cohort included a total of 6370 patients without history of ATE. The follow-up times were 3522 and 8807 person-years in the BEV-use and non-BEV use groups, respectively.
[b]Cox-proportional hazards (PHs) model adjusted for the effects of radiation, surgery, age at chemotherapy initiation, sex, hematologic comorbidity other than ATE and time-dependent use of irinotecan, oxaliplatin, and 5-FU.
*$P < 0.001$.

Table 3. Risk of cardiomyopathy (CM) and congestive heart failure (CHF) event up to 36 months of follow-up among colorectal cancer patients diagnosed from 2005 to 2007, no CM and CHF history and receiving chemotherapy with versus without bevacizumab for newly diagnosed or recurrent disease

	Event no.[a]	Event rate (per 1000 person-years)	Hazard ratio (HR, 95% CI)[b]
BEV use	53	15.44	0.97 (0.65, 1.45)
Non-BEV	126	14.55	1.0

[a]The cohort included a total of 6195 CRC patients without history of CM/CHF. The follow-up times were 3432 and 8658 person-years in the BEV-use and non-BEV use groups, respectively.
[b]Cox-proportional hazards (PHs) model adjusted for the effects of radiation, surgery, age at chemotherapy initiation, sex, cardiovascular comorbidity other than CM/CHF and time-dependent use of irinotecan, oxaliplatin, and 5-FU.

CM/CHF). The absolute rate of developing CM/CHF was 15.4 and 14.6 per 1000 person-years for CRC patients with and without BEV treatment, respectively. We did not detect an adjusted association between BEV and risk of CM/CHF (adjusted HR = 0.97, 95% confidence interval (CI) = 0.65, 1.45) (Table 3). We also did not detect any significant subgroup risk of CM/CHF.

The 3-year risk of cardiac death was 1.1%, or 78 of all 6803 CRC patients in our cohort. Unadjusted rates of cardiac death for chemotherapy-treated CRC patients with and without BEV treatment were 7.7 and 5.2 per 1000 person-years, respectively. In adjusted analysis, we noted an increased risk of cardiac death with BEV use, although the 95% CIs for the adjusted HR overlapped 1.0 (adjusted HR = 1.63, 95% CI = 0.90, 2.94) (Table 4). In a subgroup analysis by age and other stratification factors, we did not detect any statistically significant subgroup risk of cardiac death with BEV treatment.

We obtained similar results for all outcomes in our sensitivity analysis using the conventional Cox-PHs models.

Table 4. Risk of cardiac death event up to 36 months of follow-up among colorectal cancer patients diagnosed from 2005 to 2007 and receiving chemotherapy with or without bevacizumab for newly diagnosed or recurrent disease

	Event no.[a]	Event rate (per 1000 person-years)	Hazard ratio (HR, 95% CI)[b]
BEV use	29	7.73	1.63 (0.90, 2.94)
Non-BEV	49	5.15	1.0

[a]A total of 6803 patients were included in assessing the risk of cardiac death with BEV. The follow-up times were 3432 and 8658 person-years in the BEV-use and non-BEV use groups, respectively.
[b]Cox-proportional hazards (PHs) model adjusted for the effects of radiation, surgery, age at chemotherapy initiation, sex, cardiovascular comorbidity and time-dependent use of irinotecan, oxaliplatin, and 5-FU.

discussion

In this population-based cohort study, we observed an increased risk of incident ATEs associated with BEV. We found no association between BEV and incident CM/CHF events or cardiac death. Our results for cardiac deaths and CM/CHF are consistent with randomized clinical trials (RCTs) which do not report increased risk with the use of BEV. It can be reasonably assumed from current evidence that, with respect to these events, BEV is well tolerated by most patients selected to receive it.

We found a statistically significant increased HR of incident ATEs among CRC patients with no evident prior history of ATEs receiving BEV. However, this difference, when expressed in absolute terms of four additional ATEs cases per 1000 person-years, unlikely has a clinical impact since many seriously ill patients with metastatic cancer may be willing to accept an increased risk of a relatively uncommon though potentially serious side-effect in exchange for the extension of survival by a median time of 5 months [4, 7–9, 16]. We are unaware of any research on patients' perception of this tradeoff; this may be an important area for the study of patient-centered clinical decision-making.

The risk elevation for ATEs is similar to the results from randomized, clinical trials that mostly included younger populations. A recent meta-analysis of eight randomized trials, including 1096 CRC patients and 2477 patients with a variety of other advanced solid tumors, also indicated an increased risk of ATEs (HR = 1.89, 95% CI = 1.28–2.80) among BEV-treated versus non-BEV-treated CRC chemotherapy patients [28]. Additionally, a pooled analysis of two randomized trials found 7.6% and 2.8% rates of ATEs among 427 patients with metastatic CRC aged 65 years and older, with or without BEV treatment, respectively [16]. Compared with findings from these trials, we found a somewhat lower relative and absolute risk of ATEs with BEV. This may be partly attributable to careful patient selection by community practitioners aware of the potential cardiac risks associated with prescribing BEV. Evidence for this selection effect is found in Table 1, which shows that CRC patients with prior history of ATEs, CM/CHF or other cardiovascular diseases were significantly less likely to receive BEV.

While the role of BEV in the development of ATEs remains unknown, there are plausible biological mechanisms which explain it. ATEs are often caused by unstable atherosclerotic plaque and activated platelet aggregation. VEGF-A is a potent regulator of endothelial cells with known anti-apoptotic, pro-survival, and anti-inflammatory effects [29]. BEV-induced VEGF-A inhibition may adversely alter vascular homeostasis, and in turn, decrease the stability of atherosclerotic plaque, resulting in plaque rupture [30]. BEV may also reduce VEGF-A-stimulated production of important platelet inhibitors, such as nitric oxide and prostacyclin (PGI2), thus promoting arterial thrombosis, including prostaglandin I-2 and nitric oxide [31].

A clinical trial of 462 patients with metastatic breast cancer (mean age = 51) showed a higher risk (2.2%) of CHF in those receiving BEV versus those who did not (0.5%). However, our study in a much older cohort of CRC patients showed a similar absolute incidence rate and relative risk of CM/CHF for BEV-treated versus non-BEV-treated patients [14]. A pooled analysis of four clinical trials in 1142 metastatic CRC patients aged ≥65 years also failed to show any association between BEV use and CHF risk [32]. The differences of CM/CHF risk with BEV use between breast cancer and CRC patients may be partly due to less cardiotoxic treatment and fewer routine cardiac function checks in CRC versus breast cancer patients.

Our study's strengths include its large and generalizable study population. Our study cohort included sub-groups frequently excluded from randomized studies due to older age and/or predisposing medical conditions. Consequently, our findings are more generalizable to patients in general clinical practice. Additionally, the existing trials are limited by small sample sizes and therefore, lack statistical power to detect less common serious adverse events. Thus, we have provided additional and novel evidence regarding the safety of the use of BEV among advanced CRC patients aged ≥65 receiving standard chemotherapy regimens.

Our study has four limitations that should be considered when interpreting these results. First, PS analysis cannot remove all unmeasured confounding, such as that due to differences in unmeasured risk factors (e.g. smoking history or physical activity level). Second, our patient cohort definition may include patients who remained at their localized disease status. We expect that this limitation only applies to a very small proportion of the cohort and is unlikely to affect our risk estimates. Third, we relied on ICD-9 codes to identify the occurrences of ATEs and CM/CHF events. We acknowledge that the ascertainment of CHF using claims data may have high specificity (>96%) and moderate sensitivity (76%), leading to underdiagnosis of patients with CHF [33]. The misclassification may occur because the diagnosis of CHF is complicated and may often appear as a CM diagnosis. We included CM with CHF to help minimize these potential reporting errors. Finally, restricting our study population to patients without a prior history of cancer, although a sizable minority of patients with CRC, does limit the generalizability of our findings to general practice. However, this was a necessary exclusion made in order to enhance internal validity of our risk estimates for BEV by reducing related to the use of other chemotherapy agents to treat prior cancers diagnosed before age 65. Medicare claims are not available to track these agents.

In conclusion, the risk of ATEs, CM/CHF, and cardiac death in elderly patients with metastatic CRC associated with BEV is minimal. Despite the aforementioned methodological limitations, our findings from a population-based cohort treated in community practice complement existing evidence from RCTs about the safety and risks of BEV for metastatic CRC.

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disclosure

The authors have declared no conflicts of interest. LBS was an employee of NCI when the manuscript was written. She is now an employee of GlaxoSmithKline. JLM has advised and conducted clinical research for Genentech.

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