Perspective

Bevacizumab with first-line chemotherapy for Medicare patients with metastatic colorectal cancer: do the risks outweigh the benefits?

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Submitted May 25, 2012. Accepted for publication Jun 18, 2012.
DOI: 10.3978/j.issn.2224-4778.2012.06.02
Scan to your mobile device or view this article at: http://www.amepc.org/tgc/article/view/707/1880

No single randomized controlled trial (RCT) can address every possible clinical scenario in the practice of oncology. Registry studies are a valuable tool to further describe the effectiveness of an intervention when discrepancies exist between a clinical trial population and the "real world" patient population, or when additional trials are not feasible. In a recent publication, Meyerhardt *et al*. (1) analyzed the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to determine the overall survival (OS) benefit of adding bevacizumab to combination chemotherapy for Medicare patients with metastatic colorectal cancer (CRC). For Medicare patients treated between 2002 and 2007, the addition of bevacizumab to combination chemotherapy was associated with an improvement in OS from 15.9 to 19.0 months [unadjusted hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.80-0.95]. The improvement in OS remained statistically significant after adjustment for confounding variables (HR, 0.85; 95% CI: 0.78-0.93). The survival benefit of bevacizumab was most apparent in patients treated with irinotecan-based combination chemotherapy between 2002 and 2007 (HR, 0.80; 95% CI: 0.66-0.97). Interestingly, the relative survival benefit of bevacizumab appeared diminished between 2004 and 2007 (HR, 0.93; 95% CI: 0.84-1.02), and with oxaliplatin-based chemotherapy (HR, 0.96; 95% CI: 0.86 to 1.07). Bevacizumab doubled the risk of stroke and gastrointestinal perforation, but the absolute rates of these events remained low. The authors concluded that the first-line use of bevacizumab for metastatic CRC in Medicare patients is "no more than marginally effective," and is associated with a "modest excess risk of harms from perforation and stroke." Given the inherent limitations of non-randomized observational data, it is important to place the findings by Meyerhardt *et al*. in the context of other RCTs, meta-analyses, and observational studies. Information from the SEER-Medicare database contributes to our understanding of how bevacizumab affects survival, informs the discussion of the optimal first-line chemotherapy, and enhances our understanding of the toxicity of bevacizumab in patients with advanced age.

Bevacizumab was approved by the United States Food and Drug Administration (FDA) in 2004 based on an improvement in OS for patients receiving irinotecan/5-fluorouracil/leucovorin (IFL)/bevacizumab compared to IFL/placebo (2). The average age of participants in this trial was 59 years, compared to a median age at diagnosis of 69 years in the US population (3). Given higher rates of cerebrovascular accident, myocardial infarction, and angina in patients receiving bevacizumab, concern existed that the risks of bevacizumab would be greater in older patients, who have a higher background risk of these events (4). It was also unclear whether the additional bevacizumab-related adverse events outweighed a survival benefit for patients with advanced age. A randomized phase II study suggested that OS is improved in patients with advanced age receiving bevacizumab, but the benefit was not statistically significant in this underpowered trial (5). The analysis from Meyerhardt *et al*. adds to a growing body of clinical data to specifically address the risks and benefits of bevacizumab in the Medicare population.

Several phase III RCTs have evaluated bevacizumab with first line chemotherapy for patients with metastatic CRC, but none have restricted eligibility to patients with impaired performance status or advanced age. The phase

III Mitomycin Avastin® Xeloda (MAX) trial provides a useful benchmark for the survival benefits observed in the SEER-Medicare database, since the median age of patients participating in the trial was 68 years (6). The MAX trial randomized patients to either capecitabine alone, capecitabine/bevacizumab, or capecitabine/mitomycin/bevacizumab. Progression free survival (PFS), the primary endpoint, increased from 5.7 months for patients receiving capecitabine monotherapy to 8.5 months for patients receiving capecitabine/bevacizumab (HR, 0.63; 95% CI: 0.50-0.79; P<0.001). For the secondary endpoint of OS, there was a survival benefit in patients receiving capecitabine/bevacizumab versus capecitabine alone (18.9 versus 16.4 months, respectively), but this difference was not statistically significant (P=0.31). Most patients in the MAX trial received second line therapy, possibly obscuring the survival benefit of first line treatment. Despite the limitations of cross-trial comparisons, it is noteworthy that the median OS for patients receiving capecitabine/bevacizumab (18.9 months) was similar to the median OS of patients receiving chemotherapy/ bevacizumab (19.0 months) in the SEER-Medicare database, and the hazard ratio for OS was nearly identical for both studies. Since patients in the MAX trial received less intensive first-line chemotherapy than patients in the SEER-Medicare database, the similar survival may reflect the deferred use of other active therapies (irinotecan, oxaliplatin, EGRF monoclonal antibodies) in later lines of treatment. The MAX trial was underpowered to detect statistically significant survival differences, but it provides a comparable patient population to validate the relative benefit of bevacizumab for patients with advanced age.

Since most individual RCTs are underpowered to evaluate the survival benefit of chemotherapy/bevacizumab versus chemotherapy alone in patients with advanced age, investigators have pooled data from multiple RCTs. These pooled analyses further support the survival advantage of adding bevacizumab to chemotherapy. Kabbinavar *et al*. pooled survival outcomes for patients older than 65 from two placebo-controlled studies, and demonstrated an OS of 19.3 months for patients receiving chemotherapy/bevacizumab, compared to 14.3 months for patients receiving chemotherapy/placebo (HR, 0.70; 95 CI: 0.55-0.90; P=0.006) (7). In a separate pooled analysis of placebo-controlled first-line studies, the HR for survival was 0.79 (95% CI: 0.69-0.89) for patients under 65 years receiving bevacizumab, and the HR was 0.80 (95% CI: 0.67-0.97) for patients older than 70 years receiving bevacizumab (8). Both meta-analyses demonstrate a clinically meaningful survival benefit for bevacizumab, and show that the relative survival benefit is nearly equivalent between younger and older age groups.

Observational cohort studies provide another "real world" benchmark for data from RCTs. These studies are not placebo controlled, but the clinical characteristics of patients more closely reflect the general population of patients with metastatic CRC. The U.S.-based Avastin® Regimens: Investigation of Effects and Safety (ARIES) study followed survival for 424 patients who were 70 years of age or older and treated with first-line bevacizumab and chemotherapy (9). Median OS for patients 70 years of age or older in the ARIES study was 19.6 months (95% CI: 18.1-21.6 months), which once again closely approximates the OS observed in the SEER-Medicare database and other large observational cohort studies (10,11). The absence of a placebo control arm in ARIES limits the ability to draw conclusions about the relative benefit of bevacizumab.

Evidence from RCTs, meta-analyses, observational cohort studies, and registry studies support three conclusions regarding the use of bevacizumab with chemotherapy for patients with advanced age:

(I) Bevacizumab with chemotherapy improves survival for appropriately selected patients. Two RCTs have demonstrated that bevacizumab with chemotherapy extends survival for patients with metastatic CRC, and in both of these studies relatively few patients received additional treatment after progression (2,12). With greater use of effective maintenance strategies (13-15), second-line bevacizumab (12), bevacizumab beyond progression (16,17), EGFR monoclonal antibodies (18,19), and improved supportive care, the benefits of first line interventions are increasingly difficult to quantify in first line trials. A plausible explanation for the relative decrease in bevacizumab survival benefit for patients treated in the later cohort (2004-2007) in the SEER-Medicare database is the increased use of bevacizumab and other active therapies in later lines of treatment. It is difficult to account for these confounding factors in a registry study, particularly when practice patterns evolve, new therapies become available, and active therapies are either re-used or deferred to later lines of treatment.

(II) Bevacizumab can be combined with either oxaliplatin or irinotecan-based chemotherapy, but important questions remain unanswered. The SEER-Medicare database demonstrates a survival benefit for bevacizumab in combination with irinotecan-based

chemotherapy, but not oxaliplatin-based chemotherapy. A large RCT (NO16966) that enrolled patients between 2004 and 2005 also demonstrated no improvement in OS for patients receiving bevacizumab with oxaliplatin-based chemotherapy compared to chemotherapy alone (20). Given results from prior studies (2,12,21), the lack of survival benefit for bevacizumab in NO16966 was unexpected (22). A preplanned analysis from NO16966 found that patients who remained on bevacizumab until progression had longer PFS (HR, 0.63; 97.5% CI: 0.52-0.75) than the overall study population (HR, 0.83; 97.5% CI: 0.72-0.95). These results suggest that bevacizumab should be given until disease progression to maximize clinical benefit. A concern about using data obtained between 2002 and 2007 to inform clinical decisions, is that practice patterns have evolved to better manage toxicity related to bevacizumab and chemotherapy, thereby allowing more treatment to progression. Recent observational cohort studies are better positioned to incorporate these evolving practice patterns. The ARIES study indirectly compared the "real world" effectiveness of FOLFIRI/bevacizumab versus FOLFOX/bevacizumab in patients treated after 2006. PFS and OS in ARIES were similar for patients receiving FOLFIRI/ bevacizumab or FOLFOX/ bevacizumab in the first line (23). Until a RCT directly compares the efficacy of FOLFIRI/bevacizumab to FOLFOX/bevacizumab, treatment decisions will be guided by meta-analyses, observational cohort studies, and other retrospective analyses. In most of these studies, OS approaches 2 years, regardless of the first line chemotherapy backbone combined with bevacizumab (2,6,11,20,21,24-30). Additional clinical trials are needed to better understand the true benefit of oxaliplatin versus irinotecan-based combination chemotherapy, particularly when bevacizumab is given until disease progression and other contemporary maintenance strategies are applied.

(III) Bevacizumab adds to the toxicity of first-line chemotherapy, but some of these toxicities are avoidable by withholding treatment from patients at greatest risk. RCTs consistently demonstrate higher rates of treatment-related toxicity for patients receiving bevacizumab, and the SEER-Medicare database confirms this finding (1,2,4,5,12,31). The most common bevacizumab-related adverse event is hypertension, although wound-healing complications, bleeding, arterial thromboembolic events (ATEs), gastrointestinal perforation, and proteinuria are also increased. As expected, bevacizumab was associated with a doubling of gastrointestinal perforation (2.3% *vs*. 1.0%; P<0.01) and stroke risk (4.9% *vs*. 2.5%; P<0.01) in the SEER-Medicare database. Surprisingly, cardiac events were less common for patients receiving bevacizumab (11.5%) than for those receiving chemotherapy alone (14.5%). The decrease in cardiac events for patients receiving bevacizumab in the SEER-Medicare database is unexpected, and is likely a result of bias that cannot be easily accounted for in statistical analyses. Since Medicare patients were "assigned" by their treating physicians to chemotherapy/ bevacizumab or chemotherapy alone, the decreased rate of cardiac events in patients receiving bevacizumab may reflect the ability of oncologists to correctly identify patients who might be at greatest risk from anti-angiogenic therapy. Good clinical judgment, which likely introduced bias into the SEER-Medicare data, may have reduced treatment-related complications of bevacizumab.

The SEER-Medicare registry analysis from Meyerhardt *et al*. enriches our understanding of the risks and benefits of first line bevacizumab for the Medicare population. While every study design has its limitations, it is reassuring that this analysis recapitulates many findings from other first line RCTs and observational cohort studies. Available evidence demonstrates that bevacizumab improves survival in combination with first line chemotherapy, and that this survival benefit is preserved despite a modest increase in adverse events. Defining the magnitude of this survival benefit is difficult, and is likely obscured by other confounding factors. Valid concerns still exist about the utility of bevacizumab with oxaliplatin-based chemotherapy, and SEER-Medicare data do not allay those concerns. Nonetheless, the increased use of bevacizumab to progression and other maintenance strategies used in the modern-day treatment of metastatic CRC are likely not reflected in SEER-Medicare data from 2002-2007. In the absence of a RCT directly comparing bevacizumab with either oxaliplatin or irinotecan-based chemotherapy, it would be premature to change first line treatment paradigms for Medicare patients with metastatic CRC.

Acknowledgements

Disclosure: The author declares no conflict of interest.

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Cite this article as: Strickler JH. Bevacizumab with first-line chemotherapy for Medicare patients with metastatic colorectal cancer: do the risks outweigh the benefits? Transl Gastrointest Cancer 2013;2(1):39-43. DOI: 10.3978/j.issn.2224-4778.2012.06.02

