VOLUME 26 · NUMBER 28 · OCTOBER 1 2008

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Bevacizumab in Advanced Colorectal Cancer: A Challenge to the Current Paradigm

TO THE EDITOR: It is with great interest that I read the articles by Cassidy et al[1] and Saltz et al[2] describing the results of the NO16966 clinical trial. The authors are to be congratulated for conducting this large, well-designed clinical trial to address critical issues in the contemporary management of advanced colorectal cancer (CRC). The first article clearly demonstrates that capecitabine may be substituted for infusional fluorouracil in a first-line oxaliplatin-based regimen. This provides a much less cumbersome therapeutic option and will likely change practice to the benefit of our patients.

The second article reports the results of bevacizumab compared with placebo among patients receiving oxaliplatin-based chemotherapy. By demonstrating that there was no evidence of treatment interaction, the authors were able to conduct the pooled analysis of capecitabine and oxaliplatin and oxaliplatin, fluorouracil, and leucovorin with or without bevacizumab. Although the primary end point of improved progression-free survival (PFS) met statistical significance (hazard ratio, 0.83; 97.5% CI, 0.72 to 0.95; $P = .0023$), the absolute improvement in median PFS of 1.4 months is not clinically meaningful. Additionally, unlike previous randomized controlled trials (RCTs) that have evaluated bevacizumab in advanced CRC, NO16966 did not show any improvement in response rate or overall survival. As the authors note, only 5% of patients in the control arm received bevacizumab in subsequent lines of therapy, making it unlikely that the lack of survival benefit was confounded by crossover.

If this was the first large RCT to address the role of bevacizumab in advanced CRC, I suspect the authors' conclusions would be quite different. Though this trial was clearly negative and (in isolation) did not support the use of bevacizumab in this patient population, the authors present an alternative hypothesis to explain their results. Unlike previous trials, overall treatment duration of bevacizumab and placebo was similar (approximately 6 months) despite improved PFS in the experimental arm. The study protocol specified that treatment could continue until progressive disease, and thus it seems that investigators may have discontinued the study drug prematurely. The authors conclude that "treatment continuation until disease progression may be necessary to optimize the contribution of bevacizumab to therapy."[2] I was disappointed that the authors do not postulate anywhere in the article that perhaps bevacizumab is not effective in a broad patient population treated with contemporary chemotherapy.

It is important to put the results of this well-designed RCT in context by reviewing the pivotal evidence to date in support of bevacizumab. In 2004, Hurwitz et al[3] reported that the addition of bevacizumab to irinotecan, fluorouracil, and leucovorin in the first-line setting was associated with a clinically important increase in median survival of 4.7 months. In 2007, Dr Giantonio et al[4] demonstrated that bevacizumab improved median survival by 2.1 months when given with oxaliplatin, fluorouracil, and leucovorin in the second-line setting. Recently, two large international phase IV observational studies have found impressive results when bevacizumab is administered in the general population.[5,6] Finally, a non-randomized comparison between the Three Regimens of Eloxatin Evaluation (TREE) –1 and TREE-2 cohorts also suggest benefit of bevacizumab in metastatic CRC.[7] As clinicians, many of us were unsure how to interpret the data from Hurwitz et al, given that irinotecan, fluorouracil, and leucovorin is no longer standard treatment in CRC. Furthermore, the limitations of observational data and nonrandomized comparisons are well recognized. However, I believe that until the publication of NO16966, most gastrointestinal oncologists felt that bevacizumab had a clinically meaningful role in the management of patients with advanced CRC.

The results presented by Saltz et al[2] pose a considerable challenge to the current paradigm in management of advanced CRC. In many jurisdictions clinical practice has moved ahead of the evidence and bevacizumab has become standard of care in first-line management of advanced CRC. I believe that the results of NO16966 should introduce some element of uncertainty regarding the role of beavicizumab in this disease. Given the totality of the evidence, I do not propose that bevacizumab plays no role in the management of CRC. However, since the largest and most contemporary RCT has failed to demonstrate a clinically meaningful benefit to patients, I believe it would be inappropriate to accept that bevacizumab in combination when oxaliplatin-based chemotherapy is the standard of care in first-line management of metatastic CRC. Rather, this trial should encourage future studies to explore predictive biomarkers that may allow oncologists to treat patients who are likely to benefit from bevacizumab and avoid treating patients with an expensive and potentially toxic drug who are unlikely to benefit. As clinicians and investigators, we need to have an open dialogue about the true benefit of these novel anticancer therapies in the general population and distinguish results that are clinically significant from those that are only statistically significant.

Christopher Booth

Divison of Cancer Care and Epidemiology, Queen's University Cancer Research Institute, Kingston, Ontario, Canada

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Cassidy J, Clarke S, Diaz-Rubio E, et al: Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 26:2006-2012, 2008

2. Saltz LB, Clarke S, Diaz-Rubio E, et al: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J Clin Oncol 26:2013-2019, 2008

3. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004

4. Giantonio BJ, Catalano PJ, Meropol NJ, et al: Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated

metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 25:1539-1544, 2007

5. Berry S, Cunninghanm D, Michael M, et al: Preliminary efficacy of bevacizumab with first-line FOLFOX, XELOX, FOLFIRI, and fluoropyrimidines in mCRC: First BEAT. Proc Gastrointestinal Cancers Symposium, January 25-27, 2008 (abst 350)

6. Kozloff M, Sugrue M, Berlin J, et al: Safety and effectiveness of bevacizumab and chemotherapy in elderly patients with metastatic colorectal cancer: Results from the BRiTE prospective cohort study. Proc Gastrointestinal Cancers Symposium, January 25-27, 2008 (abst 345)

7. Hochster HS, Hart LL, Ramanathan RK, et al: Regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: Results of the TREE study. J Clin Oncol 21:3523-3529, 2008

DOI: 10.1200/JCO.2008.18.8060

In Reply: Dr Booth's comments regarding the report of the NO16966 trial are appreciated. We are in agreement that this large, randomized, double-blind, placebo-controlled trial adds new—and to a degree—unexpected information regarding bevacizumab in colorectal cancer (CRC) management, and that new information should be added to—and interpreted in—the context of the other trial results and information available to us on the topic. However, Dr Booth states in his letter, "If this was the first large randomized controlled trial [RCT] to address the role of bevacizumab in advanced CRC, I suspect the authors' conclusions would be quite different." Here I respectfully disagree. The conclusion of the article reads as follows: "In conclusion, this trial reached its primary objective by showing a statistically significant increase in progression-free survival [PFS] through the addition of bevacizumab to oxaliplatin-based chemotherapy in first-line metastatic CRC. No increase in response rate [RR] was seen. The observed difference in overall survival [OS] did not reach statistical significance. Continuation of bevacizumab, and most likely fluoropyrimidine therapy as well, until disease progression [DP] appears to be critical with regards to the magnitude of clinical benefit derived from bevacizumab."[1]

The statements in the conclusion are an appropriate summation of the trial results. It is outside of the scope of the article to establish what criteria should be used in defining standard treatment paradigms. However, it is well within the purview of Dr Booth and others to consider the information presented, and to challenge their assumptions regarding what should or should not be standard practice.

Are the benefits seen with the addition of bevacizumab as substantial as those seen in prior studies? Clearly not. Is the earlier discontinuation of bevacizumab a satisfactory explanation for these differences? Perhaps; it is a reasonable hypothesis, but one that is unlikely to be interrogated by another large RCT given the expense and complexity of such an undertaking. Could other factors account for these differences? Certainly. Should the findings of the NO16966 trial change the paradigm for treatment of CRC? That is a more complex question, without a clear and simple answer.

In our current drug development paradigm, success or failure is predicated on the achievement of the prespecified primary end point, in this case a statistically significant improvement in progression-free survival. That objective end point was achieved in the NO16966 trial. Dr Booth raises the important subjective question of what is a clinically meaningful improvement in PFS. This is a challenging question to answer, a challenge to which we as a cancer community of doctors, patients, industry, government, and society as a whole, have not yet risen. Dr Booth writes, "As clinicians and investigators, we need to have an open dialogue about the true benefit of these novel anticancer therapies in the general population and distinguish results that are clinically significant from those that are only statistically significant." I could not agree more. How to do this, however, is not at all clear.

The incorporation of bevacizaumab into current treatment paradigms is based on the trial reported by Hurwitz et al,[2] which showed a PFS advantage of 4.4 months and an OS advantage of 4.7 months. To those of us who treat patients and conduct clinical research, these findings may seem robust and meaningful. To a patient with CRC, however, or to family member or friend of that patient, they might seem considerably less so. In the NO16966 trial, the PFS advantage was 1.4 months. The OS benefit was also 1.4 months; however, the *P* value was .078, which did not meet the prespecified level of statistical significance, and so is a negative finding as defined in the trial (note that this does not mean there was no survival advantage; it means that the survival difference seen was only 1.4 months, and we cannot say with 95% confidence that this modest difference is due to a real drug effect, and not just due to chance; we can only say it with 92% confidence).

How then are we to interpret the findings of the NO16966 trial? Do they mean that the prior studies were wrong? No. Do they mean that there is no benefit to adding bevacizumab to the fluorouracil-leucovorin-oxaliplatin or capecitabine-oxaliplatin regimens? No, but the benefits seem to be more modest than we had hoped for; specifically, the data are most compelling that the addition of bevacizumab to front-line oxaliplatin-based therapy does not improve the response rate at all. How, then, do we reach consensus on what is clinically meaningful? Within the context of how difficult it has been to show any benefit for any new interventions in CRC, both the NO16966 trial and the Hurwitz et al trial might be regarded as clinically meaningful; within the context of what we want for our patients and what they need, arguably no colorectal trial to date fulfills the clinically meaningful criterion. Much discussion will be required to reach agreement on what a clinically meaningful improvement in a given end point is. It would be useful for such criteria to be defined in clinical trials a priori, but I fear that reaching societal consensus on the definition of clinically meaningful, if it is to be agreed that the drug will not be used if it fails to meet that prespecified clinically meaningful threshold, will be as challenging as the drug development process itself.

In the mean time, one can hardly argue with the call to develop meaningful predictive markers to allow for appropriate patient selection. However, here too we must be careful to recognize that what a predictive marker would offer in the setting of bevacizumab in CRC is to tell us who not to treat. It will not open up a new option for any CRC patient; only the development of a new effective drug would do that. What a useful predictive marker, if found, would offer to the CRC community is a more precise delineation of for whom the use of bevacizumab will not provide a benefit that is clinically meaningful.

Leonard Saltz
Department of Medicine, Memorial Sloan-Kettering Cancer Center, Gastrointestinal Oncology Service, New York, NY

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject

