Should FOLFOXIRI Plus Bevacizumab Be the Standard First-Line Therapy in Metastatic Colorectal Cancer?

RYAN D. NIPP, DAVID P. RYAN

Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Colorectal cancer is the third leading cause of cancer death in the U.S. [1]. With the advent of irinotecan, oxaliplatin, anti-EGFR, and anti-VEGF treatments, patients diagnosed with metastatic colorectal cancer can expect to live for 2 years after diagnosis, with 20% of patients alive at 5 years [2]. Most patients initially receive chemotherapy with 5-fluorouracil (5-FU), leucovorin, and either oxaliplatin (FOLFOX regimen) or irinotecan (FOLFIRI regimen) [3]. FOLFOX and FOLFIRI have equivalent efficacy in the metastatic setting, provided that patients eventually receive the alternate regimen following disease progression [3, 4]. The addition of VEGF-targeting agents to either FOLFOX or FOLFIRI can improve overall survival (OS) [5–7], and patients with KRAS wild-type (wt) tumors benefit from the addition of anti-EGFR antibody therapy [8, 9]. More than 20% of patients have metastatic disease at the time of diagnosis, and more than one-third of patients with colorectal cancer eventually develop metastases [10]. The majority of patients with metastatic colorectal cancer cannot be cured and receive palliative treatments; however, 10%–20% of patients with metastatic disease (specifically those with metastases limited to the liver) may be candidates for potentially curative surgical resection either at presentation or after a favorable response to chemotherapy [11].

In an attempt to improve response rates, to convert patients into candidates for surgical resection, and to increase survival, Italian investigators compared the regimen of 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI) with FOLFIRI in patients with unresectable metastatic colorectal cancer [12]. FOLFOXIRI consists of 5-FU administered as a 48-hour continuous infusion to a total dose of 3,200 mg/m² without a bolus, leucovorin 200 mg/m², irinotecan 165 mg/m², and oxaliplatin 85 mg/m² (Table 1). Compared with FOLFIRI, FOLFOXIRI improved response rates (RRs), progression-free survival (PFS), and OS. Despite these results, FOLFOXIRI was not widely adopted because the field had turned its collective focus to targeted therapies and had already incorporated VEGF-targeted therapy into standard first-line treatment of patients with metastatic disease [5]. Consequently, the same Italian investigators recently compared FOLFOXIRI plus bevacizumab with FOLFIRI plus bevacizumab (the Treating Patients with Metastatic Colorectal Cancer [TRIBE] trial) [13]. FOLFOXIRI plus bevacizumab, compared with FOLFIRI plus bevacizumab,

resulted in significantly higher RRs (65% vs. 53%) and PFS (median: 12.1 vs. 9.7 months). Initially, the survival advantage failed to meet statistical significance (median: 31.0 vs. 25.8 months), but updated results demonstrate a significant survival advantage (median: 29.8 vs. 25.8 months) for the TRIBE regimen [14]. Notably, secondary complete (R0) liver resection rates (15% vs. 12%) did not differ between treatment groups. Additionally, patients who received FOLFOXIRI/bevacizumab experienced higher rates of neutropenia, diarrhea, stomatitis, and peripheral neuropathy. Given these findings, should physicians caring for patients with metastatic colorectal cancer adopt the FOLFOXIRI/bevacizumab regimen as a standard first line therapy?

When considering whether FOLFOXIRI/bevacizumab is the optimal regimen for patients with metastatic colorectal cancer, the following concerns with the TRIBE trial merit discussion: (a) OS and PFS benefits in clinical trials of first line therapies are difficult to interpret, considering that other, unmeasured factors after the initial progression may influence OS; (b) the lack of genotyping and imbalance in right-sided colon cancers; and (c) the general applicability of the results to all patients with metastatic colorectal cancer. Using PFS as the primary endpoint in metastatic colorectal cancer trials seemed to be appropriate in the first-line setting when this study was started, but it is becoming evident that the PFS endpoint is problematic. Longer PFS does not always correspond with improved survival or quality of life (QOL) [15]. Furthermore, PFS is an imprecise endpoint, subject to clinical judgment, monitoring frequency, and measurement bias. And most importantly, patients' underlying disease biology and the subsequent treatment they receive may ultimately determine their OS [16–18]. Multiple factors in the setting of metastatic colorectal cancer can influence survival after progression on first-line therapy, such as (a) continued use of bevacizumab or aflibercept in second line, (b) use of anti-EGFR antibodies in patients with KRAS wt disease, (c) the use of regorafenib, and (d) the toxicity of first-line therapy preventing the delivery of subsequent lines of therapy. As is often standard practice, the TRIBE trial investigators did not control for therapy after progression on first-line treatment. Additionally, they did not systematically collect data on patients' subsequent lines of therapy, and did not collect QOL data. All of these questions

Correspondence: Ryan D. Nipp, M.D., Massachusetts General Hospital, 55 Fruit Street, Yawkey 7B, Boston, Massachusetts 02114, USA. Telephone: 617-724-4000; E-Mail: rnipp@partners.org Received December 22, 2014; accepted for publication January 2, 2015; first published online in *The Oncologist Express* on February 6, 2015. ©AlphaMed Press 1083-7159/2015/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2014-0495>

Table 1. Dosing of FOLFOXIRI compared with FOLFIRINOX

FOLFOXIRI	FOLFIRINOX
No 5-FU bolus	5-FU bolus 400 mg/m ²
5-FU 3,200 mg/m ² continuous infusion over 48 hours	5-FU 2,400 mg/m ² continuous infusion over 46 hours
Leucovorin 200 mg/m ²	Leucovorin 400 mg/m ²
Irinotecan 165 mg/m ²	Irinotecan 180 mg/m ²
Oxaliplatin 85 mg/m ²	Oxaliplatin 85 mg/m ²

Abbreviation: 5-FU, 5-fluorouracil.

raise the possibility that even OS cannot be trusted as a reliable endpoint for determining the best first-line therapy in patients with metastatic colorectal cancer.

A second concern is the lack of data regarding tumor mutational status, particularly in a study in which the arms were not well balanced regarding the site of primary tumor. Tumors with BRAF mutations are usually right-sided and can behave more aggressively than BRAF wt tumors. Notably, more patients in the experimental arm had right-sided tumors. In addition, the lack of knowledge regarding KRAS status draws into question whether subsequent anti-EGFR antibody therapy was used appropriately. The phase III FIRE-3 trial compared FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab as first-line treatment in patients with KRAS wt colorectal cancer [17]. Although RR and PFS did not differ between treatment groups, patients treated with FOLFIRI plus cetuximab experienced longer median OS (28.7 vs. 25.0 months). In contrast, results from the US Intergroup trial 80405 demonstrated no advantage for first-line cetuximab over bevacizumab when added to either FOLFOX or FOLFIRI (oncologist's choice) [18]. Nevertheless, both groups experienced median survival of more than 29 months and PFS of more than 10 months, demonstrating the importance of anti-EGFR antibody therapy in appropriately selected patients. Thus, knowledge of tumor mutational status and subsequent use of anti-EGFR antibody therapy is critically important when evaluating trials involving patients with metastatic colorectal cancer.

Finally, the TRIBE trial excluded patients over age 75 and only allowed patients over age 70 who did not have performance status limitations. These restrictions reflect concerns about the tolerability of this regimen because the investigators did not want to compromise the feasibility of using FOLFOXIRI plus bevacizumab. Elderly patients are commonly underrepresented in clinical trials [19], and by excluding these patients, investigators limit the generalizability of the data to a large proportion of colorectal cancer patients, given that the median age at diagnosis is 68 years [20].

Interestingly, FOLFOXIRI/bevacizumab did not benefit patients who received prior adjuvant treatments or those seeking a surgical resection. While the TRIBE trial was not specifically designed to answer the question of whether more patients with metastatic disease could be brought to a potentially curative resection, it remains the most compelling indication for this more aggressive regimen. Without an improvement in R0 liver resection rates, the results of the TRIBE trial do not support the use of FOLFOXIRI/bevacizumab as a means of converting patients to resection candidates. Additionally, FOLFOXIRI/bevacizumab did not benefit patients who received prior adjuvant chemotherapy, perhaps related to the development of chemoresistance [23, 24].

The TRIBE trial demonstrates several emerging principles in clinical trial design for initial treatment of metastatic colorectal cancer. First, the challenge of interpreting PFS and OS benefits with first-line therapy makes drug approval and the establishment of a "standard" in the first-line setting increasingly difficult. Second, mutational analysis is critical for understanding efficacy results in colorectal cancer clinical trials and this should be incorporated into all future clinical trials. Lastly, our ability to influence surgical resectability is limited and may have more to do with the underlying biology of the cancer and the presence of multi-organ metastases than any response to a specific therapy. FOLFOXIRI plus bevacizumab is an acceptable therapeutic option, but whether it is the best choice for our patients is still a matter of debate.

DISCLOSURES

The authors indicated no financial relationships.

REFERENCES

1. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. *CA Cancer J Clin* 2014;64:104–117.
2. Kopetz S, Chang GJ, Overman MJ et al. Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 2009;27:3677–3683.
3. Tournigand C, André T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol* 2004;22:229–237.
4. Colucci G, Gebbia V, Paoletti G et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: A multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005;23:4866–4875.
5. Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–2342.
6. Saltz LB, Clarke S, Díaz-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* 2008;26:2013–2019.
7. Hurwitz H, Tebbutt NC, Kabbinavar F et al. Efficacy and safety of bevacizumab in metastatic colorectal cancer: Pooled analysis from seven randomized controlled trials. *The Oncologist* 2013;18:1004–1012.
8. Van Cutsem E, Köhne CH, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–1417.
9. Douillard JY, Siena S, Cassidy J et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: The PRIME study. *J Clin Oncol* 2010;28:4697–4705.
10. Siegel R, Ma J, Zou Z et al. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64:9–29.
11. Folprecht G, Grothey A, Alberts S et al. Neoadjuvant treatment of unresectable colorectal liver metastases: Correlation between tumour response and resection rates. *Ann Oncol* 2005;16:1311–1319.
12. Falcone A, Ricci S, Brunetti I et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007;25:1670–1676.
13. Loupakakis F, Cremolini C, Masi G et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N Engl J Med* 2014;371:1609–1618.
14. Cremolini C, Loupakakis F, Masi A et al. FOLFOXIRI plus bevacizumab (bev) versus FOLFIRI plus bev as first-line treatment of metastatic colorectal

cancer (mCRC): Updated survival results of the phase III TRIBE trial by the GONO group. *J Clin Oncol* 2015;33(suppl 3):657a.

15. Venook AP, Tabernero J. Progression-free survival: Helpful biomarker or clinically meaningless end point? *J Clin Oncol* 2015;33:4–6.

16. Shi Q, de Gramont A, Grothey A et al. Individual patient data analysis of progression-free survival versus overall survival as a first-line end point for metastatic colorectal cancer in modern randomized trials: Findings from the analysis and research in cancers of the digestive system database. *J Clin Oncol* 2015;33:22–28.

17. Hutchins G, Southward K, Handley K et al. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. *J Clin Oncol* 2011;29:1261–1270.

18. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. *J Natl Cancer Inst* 2009;101:1642–1649.

19. Heinemann V, von Weikersthal LF, Decker T et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): A randomised, open-label, phase 3 trial. *Lancet Oncol* 2014;15:1065–1075.

20. Venook A, Niedzwiecki D, Lenz H-J. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum. *J Clin Oncol* 2014;32(5 suppl):LBA3a.

21. Lewis JH, Kilgore ML, Goldman DP et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003;21:1383–1389.

22. SEER Cancer Statistics Factsheets: Colon and Rectum Cancer. National Cancer Institute. Bethesda, MD. Available at <http://seer.cancer.gov/statfacts/html/colorect.html>. Accessed January 31, 2015.

23. Moutinho C, Martinez-Cardus A, Santos C et al. Epigenetic inactivation of the BRCA1 interactor SRBC and resistance to oxaliplatin in colorectal cancer. *J Natl Cancer Inst* 2014;106:djt322.

24. Yang AD, Fan F, Camp ER et al. Chronic oxaliplatin resistance induces epithelial-to-mesenchymal transition in colorectal cancer cell lines. *Clin Cancer Res* 2006;12:4147–4153.

For Further Reading:

Veena Shankaran, David Mummy, Lisel Koepl et al. Survival and Lifetime Costs Associated With First-Line Bevacizumab Use in Older Patients With Metastatic Colorectal Cancer. *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.