Should we move beyond VEGF inhibition in metastatic colorectal cancer? Lessons from early phase clinical trials

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Abstract: Data from recent clinical trials utilizing bevacizumab or other anti-VEGF agents in patients with metastatic colorectal cancer (mCRC) show improvements in progression-free survival (PFS) but modest, if any, improvements in overall survival (OS). Despite modest improvements, use of bevacizumab beyond first and second progression is routinely done in clinical practice. Recently, the CORRECT trial using regorafenib, a multi-kinase inhibitor with VEGF inhibitory properties, reported modest improvements in PFS and OS when compared to placebo, leading to FDA approval in the third-line setting. Prior to regorafenib, heavily pre-treated patients were often enrolled onto early phase clinical trials with many of these studies reporting efficacy amongst patients with mCRC; however, a collective efficacy analysis of mCRC patients enrolled into early phase clinical trials stratified by class of agents and their mechanism of action has not been done. To assess this, we performed an analysis of efficacy and stratified these findings based on VEGF inhibition versus non-VEGF inhibition in mCRC patients enrolled onto phase I trials at our institution from 3/2004-9/2012. Similar to many reported clinical studies, our data showed that VEGF inhibitors have a statistically significant improvement in PFS when compared to non-VEGF targeting agents; however, no differences in OS were observed between these two different classes of agents. We were not able to identify predictive biomarkers that correlate with efficacy of VEGF inhibitors. This should be further explored in prospective studies in order to identify active agents in this heavily pre-treated population that improve efficacy while minimizing cost and toxicity.

Keywords: Colorectal cancer; early phase clinical trials; VEGF inhibition

Introduction

Agents targeting the angiogenic pathway have been the cornerstone of metastatic colorectal cancer (mCRC) treatment in recent years. Standard therapy includes systemic chemotherapy, in combination or in sequence, consisting of fluoropyrimidines, oxaliplatin, and irinotecan with monoclonal antibodies that target vascular endothelial growth factor (VEGF), bevacizumab or ziv-aflibercept (1).

The benefit of adding bevacizumab was demonstrated in the AVF2017 phase III study of previously untreated patients randomized to irinotecan plus bolus fluorouracil and leucovorin (IFL) with placebo or bevacizumab (2). In 2004, the N9741 study reported that IFL was an inferior backbone compared to fluorouracil, folinic acid, and oxaliplatin (FOLFOX) (3). With subsequent studies showing equal efficacy of FOLFOX or FOLFIRI based chemotherapy, consequently bevacizumab is often combined with these chemotherapy backbones, with FOLFOX being the preferred front-line regimen amongst US clinicians (4,5). Contrary to these studies, other studies have suggested only modest efficacy benefit with bevacizumab. The NO16966 trial randomized, in a 2×2 factorial design, 1,401 previously

untreated mCRC patients either to capecitabine and oxaliplatin (XELOX) or FOLFOX4, with bevacizumab or placebo. Despite a statistically significant improvement in progression free survival (PFS), a similar improvement in overall survival (OS) was not observed (6).

In the second-line setting, the efficacy of VEGF inhibition was demonstrated in bevacizumab-naïve patients in the ECOG 3200 trial, with significant improvements in mOS and mPFS (7). In the VELOUR trial, the novel VEGF inhibitor ziv-aflibercept with FOLFIRI after progression on first-line oxaliplatin-based regimen showed improvement in mOS (8). Results of these and other studies have been the basis for the continued prominent role of VEGF inhibition in bevacizumab-naïve mCRC patients.

Furthermore, with growing reports of rebound or flare-up of angiogenesis when VEGF-targeted therapy was withheld, clinicians favored continuing anti-angiogenic therapy after initial clinical and/or radiological progression in the first or second-line setting (9,10). This notion was supported by the TML study showing improvements in mPFS and mOS, favoring bevacizumab continuation when combined with chemotherapy backbone following progression on prior chemotherapy (11). Conversely, the GONO trial randomized mCRC patients treated first-line with bevacizumab and fluoropyrimidines (FOLFIRI, FOLFOX or FOLFOXIRI) to receive mFOLFOX6 or FOLFIRI with or without bevacizumab. Although survival data are not mature, mPFS improved from 5.2 to 6.7 months with bevacizumab [hazard ratio (HR) 0.66, P=0.0072], but mOS was 16.0 versus 16.5 months (HR: 0.83, P=0.34) (12). Despite these conflicting results and modest difference in OS, many clinicians choose to continue patients on VEGF inhibitors.

With recent FDA approval of regorafenib, an oral multikinase inhibitor with angiogenic inhibition, in patients with mCRC patients who have failed standard therapies, the continued role of anti-angiogenic therapy comes to the forefront again (13). Compared to placebo, regorafenib improved mPFS from 1.7 to 1.9 months (HR: 0.49, P<0.000001) and mOS from 5.0 to 6.4 months (HR: 0.77, P=0.005), regardless of K-RAS status (14). The real question is: does this study support the continued pivotal role of anti-angiogenic inhibitors in patients with mCRC?

Prior to regorafenib approval, mCRC patients who failed standard therapies were enrolled on phase I clinical trials. Many novel agents with various mechanisms of action have demonstrated clinical efficacy amongst patients with mCRC. However, no data on pooled efficacy data analysis are available in the literature. Our institution has been conducting early phase clinical trials for over two decades. We used our large database to identify mCRC patients enrolled into phase I studies, following bevacizumab approval and prior to regorafenib approval, to determine if VEGF inhibition continued to be beneficial after first and/or second progression. We compared the efficacy results of VEGF inhibitors versus non-VEGF targeting agents.

Materials and methods

We conducted a historical cohort analysis of mCRC patients enrolled on one of 44 phase I trials at the Institute of Drug Development at the Cancer Therapy and Research Center, University of Texas Health Science Center San Antonio, Texas, from March 2004 to September 2012. All patients were 18 years of age or older. Patients had received approved standard therapies, resulting in disease progression or unacceptable toxicity. Phase I agents were classified based on the primary mechanism of action of each drug. mPFS and mOS were estimated from Kaplan-Meier curves and groups were statistically compared with the log rank test. The magnitude of association between dichotomous factors and survival was estimated with the HR.

Results

A total of 139 patients were included in the analysis with a median age of 59 years (range, 33-81 years), 67.6% were males, 91 (65.5%) were White, 44 (31.7%) were Hispanic, three (2.2%) were African American, and one (0.7%) was American Indian. Ninety-five (68.3%) had colon cancer, and 44 (31.7%) had rectal cancer. K-RAS mutations were detected in 38.7%, and 94.9% patients had ECOG performance status of 0-1. Ninety-seven (73.9%) patients had received three or more prior chemotherapy regimens, and 89.2% had prior bevacizumab treatment with 47.7% patients receiving ten or more months of bevacizumab. No patients had received prior ziv-aflibercept or regorafenib.

The 44 phase I studies included the following classes of drugs (alone or in combination): anti-angiogenic/VEGF inhibitor-27 (19.4%), cytotoxic agents-51 (36.7%), cell cycle inhibitors-17 (12.2%), tumor microenvironment inhibitors-10 (7.2%), apoptosis/autophagy inducing agents-11 (7.9%), epidermal growth factor receptor (EGFR) inhibitors-7 (5%), growth factor inhibitors-6 (4.3%), tyrosine kinase inhibitors (TKIs)-2 (1.4%), inhibitors of protein degradation-3 (2.2%), immunologic agents-2

Table 1 Efficacy analysis of subgroups of phase I agents in mCRC patients

		Progression-free survival		Overall survival	
		HR[1] (95% CI)	Log rank P	HR (95% CI)	Log rank P
Treatment	Non-VEGF targeting agent	1.00		1.00	
	VEGF inhibitors	0.60 (0.36-1.01)	0.05	1.02 (0.64-1.63)	0.92
K-RAS status in VEGF inhibitors	Mutated	1.00		1.00	
	Wild-type	0.39 (0.12-1.20)	0.09	1.08 (0.34-3.40)	0.90
K-RAS status in non-VEGF targeting agents	Mutated	1.00		1.00	
	Wild-type	1.24 (0.62-2.46)	0.53	0.72 (0.39-1.36)	0.31
Prior bevacizumab	≤3 months	1.00		1.00	
	>3 months	0.87 (0.45-1.69)	0.68	0.96 (0.52-1.77)	0.90
Age	<70 years	1.00		1.00	
	70+ years	1.47 (0.87-2.48)	0.13	1.88 (1.18-3.01)	0.007
Drug class	Cytotoxic agents	1.00		1.00	
	VEGF inhibitors	0.72 (0.41-1.27)	0.26	1.05 (0.63-1.75)	0.86
	Microtubule-stabilizing	1.00		1.00	
	VEGF inhibitors	0.50 (0.27-0.93)	0.02	0.94 (0.55-1.64)	0.84
	DNA-damaging agents	1.00		1.00	
	VEGF inhibitors	1.34 (0.62-2.93)	0.45	1.28 (0.64-2.55)	0.48
	Tumor microenvironment	1.00		1.00	
	VEGF inhibitors	0.71 (0.30-1.69)	0.43	0.60 (0.26-1.36)	0.21
	Apoptosis/autophagy	1.00		1.00	
	VEGF inhibitors	0.72 (0.29-1.79)	0.48	0.81 (0.37-1.80)	0.61
	Cell cycle inhibitors	1.00		1.00	
	VEGF inhibitors	0.33 (0.16-0.69)	0.002	0.87 (0.46-1.67)	0.68

[1], HR indicates hazard ratio.

(1.4%), inhibitors of protein folding-2 (1.4%), and cell proliferation inhibitor-1 (0.7%). Cytotoxic agents were further subdivided into 33 (23.7%) microtubule-stabilizing agents and 18 (12.9%) DNA-damaging agents.

Reasons for patients not completing study protocol included: 112 (80.6%) disease progression, 10 (7.2%) toxicity, 13 (9.4%) self-withdrawal, and 4 (2.9%) other reasons unrelated to treatment or toxicity. The numbers of cycles completed on study were: 1 cycle—38 (27.3%), 2 cycles—56 (40.3%), 3 cycles—15 (10.8%), 4+ cycles—30 (21.6%). Patients receiving VEGF Inhibitors received, on average, 2.9 cycles, whereas those receiving non-VEGF inhibitors received an average of 2.6 cycles.

The mPFS for all 139 patients with mCRC treated on phase I trials was 2.0 months (95% CI: 1.8-2.8 months). Patients treated with VEGF inhibitors (n=27) compared to non-VEGF targeting agents (n=112) had a longer mPFS of 3.7 months (95% CI: 1.8-7.4 months) versus 1.9 months

(95% CI: 1.8-2.3 months), respectively (HR: 0.60, 95% CI: 0.36-1.01, P=0.05). Nine patients were lost to follow-up and were not included in the OS analysis. The mOS for 130 patients was 6.1 months (95% CI: 5.1-6.9 months). The mOS was 6.0 (95% CI: 2.0-10.0) for patients treated with VEGF inhibitors (n=25) versus 6.2 months (95% CI: 5.1-7.0 months) for the non-VEGF targeting agents (n=105) (HR: 1.02, 95% CI: 0.64-1.63, P=0.92). Sub-group analyses were done for mPFS and mOS based on classes of agents, age, duration of prior bevacizumab therapy, and *K-RAS* status (*Table 1*).

Of the 139 patients, 45 patients (32.3%) completed three or more cycles of treatment as defined by each phase I trial protocol. At 16 weeks, 19 (13.7%) patients had either stable disease (n=16) or partial response (n=3), as defined by RECIST criteria: 22% receiving VEGF inhibitors (n=6) versus 11.6% receiving non-VEGF targeting agents (n=13). For the three partial responses, treatment was with EGFR

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inhibitor (n=1), cytotoxic/microtubule-stabilizing agent (n=1), and growth factor inhibitor (n=1).

Treatment-related adverse events (AEs) occurred in 107 (77.0%) patients, of which 34 (24.4%) patients had grade 3-4 AEs.

Discussion

VEGF inhibition has been shown to improve PFS in mCRC in the first- and second-line settings. However, the role of VEGF inhibition is unclear after disease progression has occurred on standard agents. Prior to the approval of regorafenib, fit patients were often enrolled on phase I clinical trials. In our cohort of heavily treated mCRC patients enrolled on phase I trials after failure of standard treatments, including progression on bevacizumab, we observed a mPFS of 2.0 months and mOS of 6.1 months. Although comparison between studies should be viewed with caution, our data appears somewhat similar to the mPFS of 1.9 months and mOS of 6.2 months seen with regorafenib (14). In our cohort, we observed that patients treated with VEGF inhibitors had longer mPFS (3.7 months) compared to non-VEGF targeting agents (1.9 months). However, mOS was not statistically different (6.0 versus 6.2 months, respectively), suggesting a role for VEGF inhibition in disease stabilization. Although this did not translate to better mOS in our cohort, it mirrors clinical findings reported in some first-line and second-line studies utilizing VEGF agents (12,15). In the third-line setting, even when statistical significance is reached, as was seen with regorafenib *vs.* placebo, gains in PFS and OS were modest; i.e., 0.2 months (6 days) improvement in mPFS and 1.4 months (42 days) benefit in mOS (14). It is likely some patients do derive benefit from regorafenib, however, without robust predictive markers of response, the role for continued VEGF inhibition after disease progression on bevacizumab remains unclear.

In this as well as in other settings, improved PFS does not always translate to improved OS. From studies of bevacizumab in metastatic breast cancer, we have seen a reversal of FDA approval of bevacizumab, due in part to a lack of improvement in OS (16-18). This reversal raised the controversy around the inability to improve OS when powering studies for the primary endpoint of tumor response and PFS rather than OS (19). However, even with a statistically significant positive trial, such as with regorafenib, the absolute benefit in OS may be outweighed by the cost and toxicity of treatment. Thus, along with efficacy, cost and absolute differences in survival should play a role in the FDA approval of new agents.

In our cohort, we did not detect any predictive factors that would identify patients benefiting from VEGF inhibition. Our analysis showed that *K-RAS* status and duration of prior bevacizumab therapy did not affect efficacy outcomes. If mCRC patients who would benefit from VEGF inhibition could be identified by predictive biomarkers, treatment would become more efficacious and cost-effective. Recently, the AVAGAST trial demonstrated that plasma VEGF-A and tumor neuropilin-1 predict clinical outcome in patients with advanced gastric cancer treated with bevacizumab (20). For mCRC patients receiving bevacizumab, low levels of baseline angiopoetin-2, a key regulator of vascular remodeling in conjunction with VEGF, has been associated with better survival (21,22). Appropriate predictive biomarkers should be incorporated prospectively into early phase clinical trials in order to identify a subset of mCRC patients who would benefit from VEGF inhibition.

Our study is limited by having a heterogeneous population that was not randomized nor controlled between the two comparative groups; however, this retrospective analysis demonstrates the need to evaluate new agents in mCRC and to look beyond VEGF inhibition.

Acknowledgments

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