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Bevacizumab-Based Therapies in the First-Line Treatment of Metastatic Colorectal Cancer

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ABSTRACT

Since its approval for the first-line treatment of metastatic colorectal cancer (mCRC), bevacizumab has become a standard treatment option in combination with chemotherapy for patients with mCRC. Bevacizumab has demonstrated efficacy in combination with a number of different backbone chemotherapy regimens, and its widespread use has introduced several important questions regarding the selection and optimization of bevacizumab-based treatment regimens, its use in various patient populations, and the identification of associated adverse events. This review discusses the results of several phase II and phase III clinical trials, as well as large observational studies, to address the use of bevacizumab in the treatment of patients with mCRC in the first-line setting. *The Oncologist* 2012;17:513–524

INTRODUCTION

The U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) for the first-line treatment of patients with metastatic colorectal cancer (mCRC) in 2004. Subsequently, bevacizumab became a standard first-line treatment option in combination with chemotherapy. Despite nearly a decade of experience with bevacizumab, important questions still remain regarding its optimal use, the ideal patient population, potential adverse events, and predictive biomarkers of response. This review discusses the selection and optimization of bevacizumab-based chemotherapy regimens in the first-line treatment of patients with mCRC.

BEVACIZUMAB: AN OVERVIEW

Tumor-related blood vessels depend on vascular endothelial growth factor (VEGF or VEGF-A) for growth and survival. Bevacizumab is a recombinant humanized monoclonal IgG_1 antibody that neutralizes VEGF-A and prevents its binding to VEGF receptor 2 (VEGFR-2), its primary receptor. This blockade inhibits endothelial cell responses related to permeability, proliferation, migration, and survival [1]. Bevacizumab inhibits tumor angiogenesis, growth, and metastasis in numerous tumor models [2–8] while reducing intratumoral interstitial pressure, thereby potentially promoting the delivery of cytotoxic chemotherapy [9]. Bevacizumab has several other proposed mechanisms of action, many of which have been extensively reviewed [10–13]. Several other anti-VEGF agents have been tested for the treatment of mCRC, although none are currently approved by the FDA [14–19].

Initial phase I studies with bevacizumab demonstrated favorable tolerability [20, 21]. The plasma half-life is ~20 days, which allows dosing every 2 or 3 weeks. Bevacizumab has demonstrated clinical benefit for patients with multiple cancers, leading to regulatory approvals for its use in mCRC, non-

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small cell lung cancer, renal cell cancer, and glioblastoma. Its approval for breast cancer was recently rescinded by the FDA, but the National Comprehensive Cancer Network Breast Cancer Guidelines Panel has so far affirmed its support for bevacizumab with paclitaxel as a first-line treatment option for metastatic breast cancer [22].

Current Questions on the Optimal Use of Bevacizumab in First-Line Treatment

Chemotherapy Backbone

For mCRC, bevacizumab has demonstrated clinical benefit in combination with fluoropyrimidines alone and with fluoropyrimidines combined with either oxaliplatin or irinotecan. In the U.S., bevacizumab is FDA approved with infusional 5-fluorouracil (5-FU), whereas in Europe and many other countries, bevacizumab is approved with oral or infusional 5-FU. A partial listing of key clinical trials of bevacizumab in the first-line setting is shown in Table 1, and the incidence rates of key bevacizumab-related adverse events are listed in Figure 1.

The phase III trial AVF2107g, which led to the initial approval of bevacizumab by the FDA, compared first-line irinotecan, bolus 5-FU, and leucovorin (LV) (the IFL regimen) with and without bevacizumab in patients with mCRC. In that study, the overall survival (OS) and median progression-free survival (PFS) times were longer in the IFL–bevacizumab arm [23]. The phase III Bevacizumab plus Irinotecan in Colorectal Cancer (BICC-C) clinical trial further clarified the optimal irinotecan-based regimen in combination with bevacizumab for first-line mCRC by comparing infusional 5-FU, LV, and irinotecan (FOLFIRI) plus bevacizumab with IFL plus bevacizumab [24, 25]. Patients in the FOLFIRI–bevacizumab had a longer median OS time than those in the IFL–bevacizumab arm. On the basis of this and other studies, FOLFIRI has largely replaced IFL as the preferred irinotecan-based backbone for bevacizumab. In the U.S., the combination of capecitabine and irinotecan (XELIRI) with bevacizumab has not been well studied at doses and schedules that are tolerable in patients. The XELIRI regimen has been studied more extensively in Europe [26–31].

The clinical benefit of bevacizumab combined with a fluoropyrimidine and oxaliplatin has been evaluated in several randomized trials [32, 33]. In the phase III NO16966 study, 1,401 patients were randomized in a two-by-two design to capecitabine and oxaliplatin (XELOX) compared with 5-FU, LV, and oxaliplatin (FOLFOX4) [33]. Both arms were further randomized to bevacizumab or placebo. Pooled outcomes from the chemotherapy–bevacizumab arm were compared with those from the chemotherapy–placebo arm. The addition of bevacizumab to chemotherapy resulted in a longer median OS time, 21.3 months versus 19.9 months, but this difference was not statistically significant (hazard ratio [HR], 0.89; $p = .077$). The response rates (RRs) were also similar in the two groups. There was a modestly longer median PFS interval for patients receiving bevacizumab than for those given placebo; this result was statistically significant (HR, 0.83; $p = .002$). Given the OS benefits observed with first-line IFL–bevacizumab [23] and with FOLFOX–bevacizumab in the second-line setting [34], the results of the NO16966 trial were surprising. Clinical outcomes in the NO16966 trial may have been influenced by high rates of treatment discontinuation prior to disease progression in both the bevacizumab and control groups (71% and 53%, respectively). The reasons for treatment discontinuation are not well understood but are likely related to the difficulties of remaining on prolonged therapy, including the complications of cumulative toxicities and the need to remain on protocol-defined treatment schedules. A preplanned analysis that adjusted for patient dropout for reasons other than death or disease progression demonstrated an HR for progression of 0.63 with chemotherapy plus bevacizumab compared with chemotherapy plus placebo. This difference has several implications. First, it emphasizes issues that complicate the interpretation of PFS outcomes. If a large fraction of patients stop protocol-defined therapy before progression, treatment benefits may be diluted. Second, it emphasizes the need for protocol-defined treatments to be more flexible and sustainable, particularly when patients may require prolonged treatment.

In clinical practice, the decision of which chemotherapy to combine with bevacizumab is often guided by practical considerations of convenience, cost, and patient preference. The XELOX–bevacizumab combination offers the convenience of infusions every 3 weeks, albeit with slightly higher rates of hand–foot symptoms and gastrointestinal toxicity. For patients remaining on treatment for a prolonged period, the convenience of less frequent infusion visits may be particularly attractive. Alternatively, the FOLFOX–bevacizumab combination may be better tolerated in some patients but requires an ambulatory infusional device and more frequent chemotherapy administration. The FOLFIRI–bevacizumab combination also requires infusion visits every 2 weeks, limiting the long-term convenience of this regimen.

Regardless of the chemotherapy backbone, patients treated with first-line chemotherapy plus bevacizumab consistently experience a median PFS interval in the range of 9–12 months and a median OS time of ~2 years. These results have been replicated in the control arms of several trials, including the Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer (CAIRO)2, Panitumumab Advanced Colorectal Cancer Evaluation (PACCE), and HORIZON III trials [35–37]. Additionally, community-based observational registry studies have demonstrated PFS and OS results comparable with results obtained in randomized trials. In those studies, the doses and schedules of treatments are at the discretion of the physician, assessments of disease response and progression are based on clinician judgment rather than formal criteria, and broader conclusions about safety and efficacy are limited by the absence of a control arm. Observational registry studies are a useful way of benchmarking experiences reported in formal randomized trials and of exploring questions related to the impact of practice variance, which is minimized in formal trials. The Bevacizumab Regimens' Investigation of Treatment Effects (BRiTE) study prospectively evaluated the clinical outcomes of patients receiving bevacizumab combined with

Table 1. Efficacy outcomes from clinical trials of BV plus CT regimens in the first-line treatment of mCRC

Study	Phase	CT backbone	CT dosing	BV dosing	*n* of patients in BV arm	RR in BV arm, %	Median PFS, mos[a]	Median OS, mos[a]
AVF2107g [23]	III	IFL	5-FU (500 mg/m^2 i.v. bolus), LV (20 mg/m^2 i.v. bolus), irinotecan (125 mg/m^2 i.v. bolus); administered weekly for the first 4 wks of each 6-wk cycle	5 mg/kg q2w	402	44.8	10.6 versus 6.2 (HR, 0.54; $p <$ .001)	20.3 versus 15.6 (HR, 0.66; $p <$ .001)
AVF2192g [43]	II	IFL	5-FU (500 mg/m^2 bolus), LV (500 mg/m^2 infusion); administered weekly for the first 6 wks of each 8-wk cycle	5 mg/kg q2w	104	26.0	9.2 versus 5.5 (HR, 0.50; 95% CI, 0.34–0.73)	16.6 versus 12.9 (HR, 0.79; 95% CI, 0.56–1.10)
BICC-C [24, 25]	III	FOLFIRI	5-FU (400 mg/m^2 i.v. bolus), LV (400 mg/m^2 i.v. over 2 hours), irinotecan (180 mg/m^2 i.v. over 90 minutes), 5-FU (2,400 mg/m^2 i.v. continuous infusion over 46 hours); administered q2w	5 mg/kg q2w	57	57.9	11.2	28.0
		Modified IFL	5-FU (500 mg/m^2 i.v. bolus), LV (20 mg/m^2 i.v. bolus), irinotecan (125 mg/m^2 i.v. over 90 minutes); administered on days 1 and 8 of each 3-wk cycle	7.5 mg/kg q3w	60	53.3	8.3	19.2
ARTIST [98]	III	Modified IFL	5-FU (500 mg/m^2 i.v. bolus), LV (20 mg/m^2 i.v. bolus), irinotecan (125 mg/m^2 i.v. bolus); administered weekly for the first 4 wks of each 6-wk cycle	5 mg/kg q2w	139	35.3	8.3 versus 4.2 (HR, 0.44; 95% CI, 0.31–0.63)	18.7 versus 13.4 (HR, 0.62; 95% CI, 0.41- 0.95)
NO16966 [33]	III	FOLFOX4	LV (200 mg/m^2 i.v. over 2 hours), oxaliplatin (85 mg/m^2 i.v. over 2 hours), 5-FU (400 mg/m^2 i.v. bolus), followed by a 22-hour continuous infusion of 5-FU (600 mg/m^2); administered q2w	5 mg/kg q2w	699	47.0	9.4 versus 8.0 (HR, 0.83; 95% CI, 0.72–0.95)	21.3 versus 19.9 (HR, 0.89; 95% CI, 0.76–1.03)
		XELOX	Oxaliplatin (130 mg/m^2 i.v. over 2 hours on day 1), capecitabine (1,000 mg/m^2 orally, twice daily on days 1–14); administered on a 21-day cycle	7.5 mg/kg q3w				
TREE-2 [32]	II	mFOLFOX6	LV (350 mg/m^2 i.v. over 2 hours), oxaliplatin (85 mg/m^2 i.v. over 2 hours), 5-FU (400 mg/m^2 i.v. bolus), followed by a 46-hour continuous infusion of 5-FU (2,400 mg/m^2); administered q2w	5 mg/kg q2w	71	52.0	9.9	26.1
		bFOL	Oxaliplatin (85 mg/m^2 i.v. on days 1 and 15), LV (20 mg/m^2 i.v. over 10–20 minutes on days 1, 8, and 15), 5-FU (500 mg/m^2 i.v. push on days 1,8, and 15); administered q4w	5 mg/kg q2w	70	49.0	8.3	20.4
		XELOX	Oxaliplatin (130 mg/m^2 i.v. on day 1), capecitabine[b] (850 mg/m^2 orally, twice daily on days 1–15); administered q3w	7.5 mg/kg q3w	72	36.0	10.3	24.6
		All BV arms combined			213	–	-	23.7 versus 18.2 (95% CI, 21.3–26.8)
MAX[c] **[45]**	III	Capecitabine	Capecitabine (1,250 mg/m^2 orally, twice daily on days 1–15); administered q3w	7.5 mg/kg q3w	157	56.0	8.5 versus 5.7 (HR, 0.63; 95% CI, 0.50–0.79)	-
CAIRO-2[d] [36]	III	Capecitabine + oxaliplatin	Capecitabine (1,000 mg/m^2 orally, twice daily on days 1–14) Oxaliplatin (130 mg/m^2 i.v. on day 1); administered q3w	7.5 mg/kg q3w	368	50.0	10.7	20.3
PACCE[e] [35]	III	Oxaliplatin-based	Investigator's choice	Investigator's choice	410	48.0	11.4	24.5
		Irinotecan-based			115	40.0	11.7	20.5

[a]The median PFS and OS times are reported for the bevacizumab-containing arm versus the control arm, respectively.
[b]The capecitabine dose was reduced from 1,000 mg/m^2 in the TREE-1 study.
[c]BV + capecitabine + mitomycin arm excluded from this table.
[d]Data shown are from the capecitabine + oxaliplatin + BV control arm only.
[e]Data shown are for the two nonpanitumumab control arms.
Abbreviations: 5-FU, 5-fluorouracil; bFOL, bolus FU and low-dose LV with oxaliplatin; BICC-C, bevacizumab plus irinotecan in colorectal cancer; BV, bevacizumab; CAIRO, capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer; CI, confidence interval; CT, chemotherapy; FOLFIRI, 5-FU, LV, and irinotecan; FOLFOX, 5-FU, LV, and oxaliplatin; HR, hazard ratio; IFL, irinotecan, 5-FU, and LV; LV, leucovorin; MAX, Mitomycin Avastin® Xeloda; mCRC, metastatic colorectal cancer; OS, overall survival; PACCE, panitumumab advanced colorectal cancer evaluation; PFS, progression-free survival; PO, orally; q2w, every 2 weeks; q3w, every 3 weeks; RR, response rate; TREE, three regimens of eloxatin in advanced colorectal cancer; XELOX, capecitabine plus oxaliplatin.

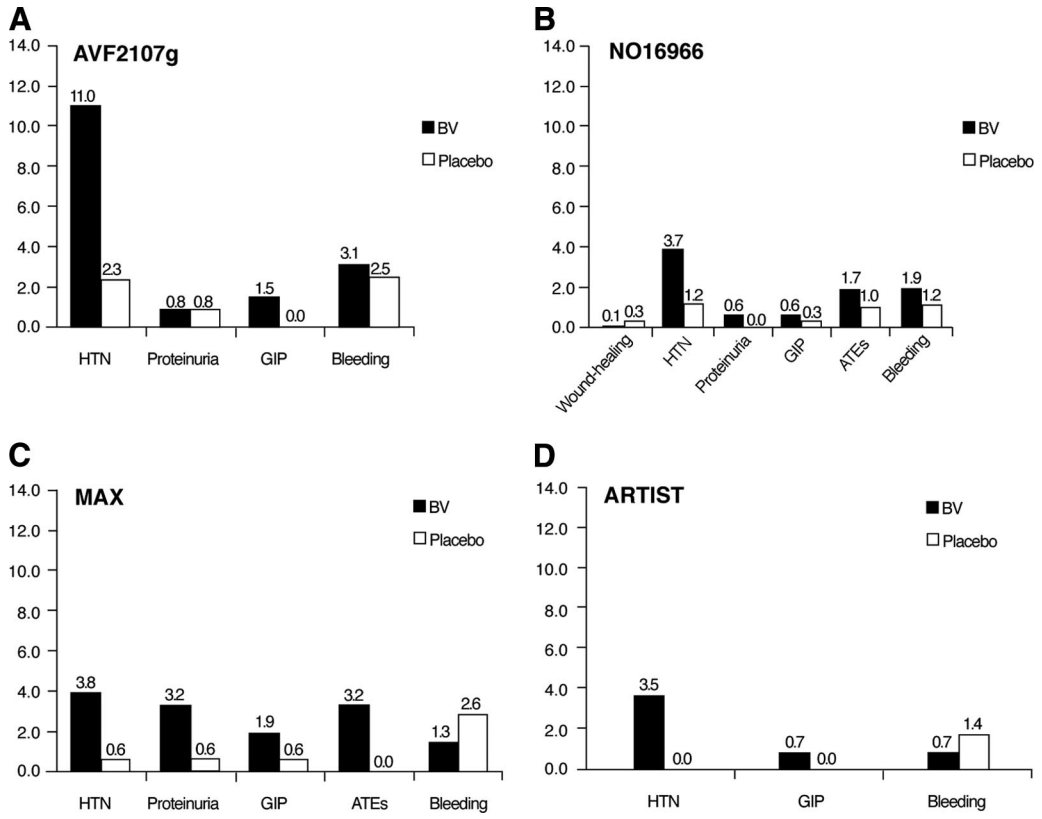

Figure 1. Incidence of key bevacizumab-related adverse events in selected phase III randomized clinical trials.

Abbreviations: ATE, arterial thromboembolism; BV, bevacizumab; GIP, gastrointestinal perforation; HTN, hypertension; MAX, Mitomycin Avastin® Xeloda.

chemotherapy for the first-line treatment of mCRC [38]. Investigators enrolled 1,953 patients from 248 primarily community-based sites in the U.S. A total of 96% of patients received bevacizumab every 2 weeks, with the majority receiving FOLFOX plus bevacizumab. The median OS duration for patients receiving first-line FOLFOX–bevacizumab treatment was 24.4 months (95% confidence interval [CI], 22.6–26.0 months), and the median OS time with first-line FOLFIRI plus bevacizumab was 22.9 months (95% CI, 19.6–27.4 months).

Similar OS and PFS results were observed in other large observational studies, including the U.S.-based Avastin® Regimens: Investigation of Effects and Safety (ARIES) trial, a study of first- or second-line bevacizumab for mCRC, and the international Bevacizumab Expanded Access Trial (BEAT), a nonrandomized study of the safety and efficacy of bevacizumab with first-line chemotherapy [39, 40]. In the ARIES study, the 715 patients receiving first-line FOLFOX plus bevacizumab had a median time to progression (TTP) and OS time of 9.7 and 23.5 months, respectively [41]. The 182 patients receiving FOLFIRI plus bevacizumab had a median TTP of 9.3 months and a median OS time of 26.3 months. Because there is no conclusive evidence that bevacizumab has superior activity when combined with a specific chemotherapy and rates of serious adverse events are similar for patients receiving FOLFOX, FOLFIRI, or XELOX, all these chemotherapy backbones may be considered appropriate for combination with bevacizumab in the first-line treatment setting.

For patients who are poor candidates for oxaliplatin or irinotecan, clinical trial evidence supports the use of bevacizumab with 5-FU and LV alone. A randomized phase II trial comparing 5-FU, LV, and bevacizumab with 5-FU, LV and placebo demonstrated a longer median OS time for the FU–LV–bevacizumab group of 16.6 months, versus 12.9 months for the 5-FU–LV–placebo group, but this difference did not reach statistical significance ($p = .16$). The PFS times were 5.5 months in the placebo-containing arm and 9.2 months in the bevacizumab-containing arm, which was statistically significant ($p < .01$) [42, 43]. A follow-up pooled analysis of three randomized studies comparing 5-FU with and without bevacizumab demonstrated a longer median OS time for patients receiving 5-FU with bevacizumab than for those receiving 5-FU alone ($p = .008$) and a statistically significant higher overall RR ($p = .019$) [44].

Similar benefits were seen in the Mitomycin Avastin® Xeloda (MAX) trial, a phase III study of capecitabine alone, capecitabine plus bevacizumab, and capecitabine, mitomycin, and bevacizumab [45]. Although the longer OS time for patients receiving capecitabine plus bevacizumab was not statistically

significantly different from that seen with capecitabine alone, the median PFS intervals were 5.7 months for the capecitabine monotherapy arm and 8.5 months for the capecitabine–bevacizumab arm ($p < .01$). Taken together, the data from these studies support the use of single-agent 5-FU or capecitabine with bevacizumab in patients who are not candidates for combination chemotherapy but who are otherwise suitable for treatment.

Maintenance Treatment

Decisions about the duration of first-line chemotherapy, treatment breaks, and the use of maintenance chemotherapy remain controversial. The goal of maintenance therapy is to ensure sufficient tumor suppression while maintaining quality of life. Most combination chemotherapy regimens cannot be continued indefinitely without significant modification or interruption. Several clinical trials, such as the optimized leucovorin [LV]-fluorouracil [FU]-oxaliplatin (OPTIMOX)-1 and OPTIMOX-2 studies, offered modest support for the continuation of chemotherapy as tolerated, but bevacizumab was not included in those studies [46–48]. Most clinical trials studying bevacizumab have continued treatment as tolerated until disease progression [33, 34, 49]. To specifically address the issue of maintenance therapy with bevacizumab, the Maintenance in Colorectal Cancer (MACRO) study evaluated the clinical benefit of XELOX plus bevacizumab until progression compared with XELOX plus bevacizumab for six cycles followed by maintenance bevacizumab alone [50]. Many of the patients in the XELOX–bevacizumab arm stopped oxaliplatin because of cumulative toxicity, resulting in capecitabine and bevacizumab being given as unofficial maintenance therapy in that arm. Interim results, reported at a median follow-up of 16 months, demonstrated a modest PFS advantage for the XELOX–bevacizumab group (HR, 1.1; 95% CI, 0.89–1.37; $p = .59$). As expected, there were also higher rates of hand–foot syndrome and neuropathy in the group receiving continuous XELOX plus bevacizumab. Outside a clinical trial, the standard approach of continuing otherwise effective therapy is to simply modify or reduce the agents causing toxicity, with the goal of preempting severe or otherwise unacceptable toxicities. Several ongoing clinical trials are further addressing the issue of maintenance therapy with bevacizumab (Table 2) [51–55].

Bevacizumab Beyond First Progression

Data from the observational BRiTE study were used to compare clinical outcomes for patients with mCRC who received bevacizumab beyond progression after first-line treatment [56]. Compared with the group receiving additional treatment without bevacizumab (median OS time, 19.9 months), patients receiving bevacizumab beyond first progression had a significantly longer median OS time (31.8 months; HR, 0.48; $p < .001$). The ARIES study also provided valuable information regarding the clinical outcomes of patients in community practice receiving bevacizumab beyond first progression. The median survival duration beyond progression for patients continuing bevacizumab was 14.1 months, compared with 7.5 months for patients receiving additional treatment without bevacizumab (HR, 0.52; $p < .001$) [39]. Because both the ARIES and BRiTE studies were not randomized, these findings may be a result of biases related to patient selection and management (patients with more indolent disease stay on treatment longer) or a true treatment effect. Randomized clinical trials designed to follow up these findings and formally test the clinical benefit of bevacizumab beyond progression are ongoing [57–59].

Bevacizumab and Resection of Metastatic Disease With Curative Intent

Approximately one third of patients with mCRC have disease confined to the liver, and surgical metastatic resection is an important option for a subset of these patients [60]. Of the patients who receive liver metastasectomy with curative intent, up to 40% are alive at 5 years and 25% are alive at 10 years [61]. Preoperative conversion chemotherapy may be needed to convert patients with borderline-resectable disease to resectable disease. Currently, there are no data to suggest that one conversion chemotherapy regimen is superior to another. In addition, cross-study comparisons are particularly problematic because resectability can depend on local surgical expertise as well as the exact size, number, and location of the liver metastases.

The clinical benefit of adding bevacizumab to preoperative chemotherapy is not defined. The safety and efficacy of preoperative bevacizumab were assessed in a post hoc analysis of the NO16966 and First BEAT clinical trials [62]. In the subset of patients with metastases limited to the liver, 12.3% of patients receiving chemotherapy plus bevacizumab (26 of 211) eventually received a R0 resection, compared with 11.6% of patients (24 of 207) treated with chemotherapy plus placebo ($p = .81$). Additional phase II studies and case series have evaluated preoperative bevacizumab with chemotherapy for patients with liver-only disease, with encouraging rates of conversion to resectability (Table 3) [61, 63, 64]. Practice patterns for the use of preoperative bevacizumab vary. When patients receive preoperative bevacizumab, the treatment is typically stopped 6–8 weeks before surgery to minimize bleeding and wound-healing complications.

Toxicity

Initial phase III clinical trials studying bevacizumab compared with placebo noted slightly higher rates of bleeding, arterial thromboembolic events (i.e., cerebral vascular events, myocardial infarction, transient ischemic attack, and angina), gastrointestinal perforation, altered wound healing, proteinuria, and hypertension. These adverse events are now largely considered anti-VEGF class toxicities. In the AVF2107g clinical trial, grade 3–5 (severe, life-threatening, and lethal) adverse events were more common in the bevacizumab arm than in the placebo arm (85% versus 74%), but most of these additional toxicities were readily manageable [23]. The most common bevacizumab-associated adverse event was hypertension, with 11% of patients developing grade 3 hypertension, compared with 2% of patients receiving placebo. Grade 3 hypertension

Table 2. Key and ongoing trials investigating BV as maintenance therapy for mCRC

Study	Phase	Induction CT	Arm	Maintenance regimen	Median PFS, mos	Median OS, months
MACRO [50]	III	XELOX + BV (6 cycles)	1	XELOX + BV ($n = 239$)	10.4	23.4
			2	BV ($n = 241$)	9.7	21.7
NCT00623805 [51]	III	XELOX + BV(6 cycles)	1	XELOX + BV ($n = 61$)	8.3	Not reported
			2	Capecitabine + BV ($n = 61$)	9.9	
CAIRO-3 [54]	III	XELOX + BV (6 cycles)	1	Observation	Trial ongoing	Trial ongoing
			2	Capecitabine (daily) + BV		
DREAM [55]	III	mFOLFOX + BV or XELOX + BV (6 cycles)	1	Erlotinib + BV	Trial ongoing	Trial ongoing
			2	BV		
ClinicalTrials.gov identifier, NCT00952029 [52]	II	FOLFIRI + BV (12 2-wk courses)	1	Observation	Trial ongoing	Trial ongoing
			2	BV		
ClinicalTrials.gov identifier, NCT00544700 [53]	III	First-line CT + BV (up to 24 wks)	1	Observation	Trial ongoing	Trial ongoing
			2	BV		

Abbreviations: BV, bevacizumab; CAIRO, capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer; CT, chemotherapy; DREAM, double inhibition reintroduction erlotinib avastin in metastatic colorectal cancer; FOLFIRI, irinotecan with infusional 5-fluorouracil and leucovorin; MACRO, Maintenance in Colorectal Cancer; mFOLFOX, modified oxaliplatin with infusional 5-fluorouracil and leucovorin; XELOX, capecitabine and oxaliplatin.

Table 3. Studies evaluating bevacizumab in patients with CRC liver metastases

Study	Phase	Patient population	Arm 1	Arm 2	Response rate, %	Resectability rate, %
Wong et al. [63]	II	Patients unsuitable for upfront resection of liver-only metastases	CAPEOX + BV ($n = 45$)	NA	OR, 78%; 95% CI, 63%–89%	40% (12/30) in patients with nonsynchronous metastases; 66% (10/15) in patients with synchronous metastases
Bertolini et al [61]	II	Patients with nonoptimally resectable CRC liver metastases	FOLFOX6 + BV ($n = 21$)	NA	OR, 57.1% (13/21); pCR, 14% (3/21)	61.9% (13/21)
Ribero et al [64]	Case series	Patients consecutively treated preoperatively with 5-FU + oxaliplatin for CRC liver metastases	5-FU + oxaliplatin ($n = 43$)	5-FU + oxaliplatin + BV ($n = 62$)	Pathologic response,[a] 23% versus 45%; pCR, 11.6% versus 11.3% (arm 1 versus arm 2, respectively)	NR

[a]Defined as <25% residual viable tumor cells.
Abbreviations: 5-FU, 5-fluorouracil; BV, bevacizumab; CAPEOX, capecitabine with oxaliplatin; CI, confidence interval; CRC, colorectal cancer; FOLFOX, oxaliplatin with infusional 5-FU and leucovorin; NA, not applicable, NR, not reported; OR, objective response; pCR, pathologic complete response.

was defined as blood pressure requiring adjustment with an antihypertensive medication. No grade 4 or 5 hypertensive events were seen in that study. Many of the adverse events attributable to bevacizumab in the AVF2107g trial occurred infrequently. The use of bevacizumab was associated with a 3.1% risk for severe bleeding (versus 2.5% for placebo) and a 1.5% rate of gastrointestinal perforation (versus none for placebo). Other grade ≥3 toxicities attributed to bevacizumab included arterial thromboembolic events (2% versus 1%), wound-healing complications (1.3% versus 0.5), and proteinuria (any proteinuria, 26% versus 21%, but no difference in grade 2 or 3 proteinuria) [1, 65, 66]. The incidence rates of adverse events were similar in the NO16966 clinical trial (Table 4 and Fig. 1).

Although the AVF2107g study did not show an association between bevacizumab and the risk for venous thromboembolism (VTE), a meta-analysis of four placebo-controlled studies of chemotherapy with and without bevacizumab suggested a potential risk for VTE in patients receiving antiangiogenic therapy [67]. However, a large pooled analysis using patient-specific data from 10 placebo-controlled trials of chemother-

Table 4. Incidence of selected bevacizumab-related adverse events observed in the BRiTE, BEAT, and ARIES trials and in the BV-containing arm of the AVF2107g and NO16966 trials

Adverse event (grade 3–5)	AVF2107g [23] IFL + BV arm (n = 393)	NO16966 [33] FOLFOX4–XELOX + BV arm (n = 694)	BRiTE [38] CT + BV (n = 1,953)	First BEAT [40] CT + BV (n = 1,914)	ARIES [39] CT + BV (n = 1,041)
Bleeding, %	3.1	2.0	2.2	3.2	2.9
GI perforation, %	1.5	<1	1.9	1.9	0.3
ATEs, %	NR	2[a]	2.0	1.5	2.1
Wound-healing complications, %	2.1	<1	4.4	4.0	NR
Hypertension, %	11.0	4.0	22[b]	5	9.2[b]

[a]Includes ischemic cardiac events.
[b]New or worsened hypertension (requiring medication).
Abbreviations: 5-FU, 5-fluorouracil; ARIES, Avastin® Regimens: Investigation of Effects and Safety; ATE, arterial thromboembolism; BEAT, Bevacizumab Expanded Access Trial; BRiTE, Bevacizumab Regimens' Investigation of Treatment Effects; BV, bevacizumab; CT, chemotherapy; FOLFOX, leucovorin, 5-FU, and oxaliplatin; GI, gastrointestinal; IFL, irinotecan, bolus 5-FU, and leucovorin; NR, not reported; XELOX, capecitabine and oxaliplatin.

apy with and without bevacizumab found no difference in the risk for VTE in patients receiving bevacizumab compared with placebo [68]. VTE remains a significant concern for all patients with mCRC [69]. Nonetheless, bevacizumab does not appear to increase the risk for VTE or the risk for bleeding while on anticoagulation. On the basis of these data, bevacizumab is considered an appropriate option in patients with a history of VTE and in patients who are receiving well-monitored anticoagulation.

The incidence rates of adverse events for first-line bevacizumab in observational studies have generally mirrored results from placebo-controlled studies (Table 4). The observed rate of arterial thromboembolic events for patients receiving bevacizumab in the BRiTE study was comparable with the rate observed in other phase III clinical trials [38, 70]. De novo hypertension and worsening hypertension were common adverse events, but most hypertension events were controlled with routine medical management. One case of proteinuria was reported. These clinical outcomes were similar to what was observed in the ARIES, First BEAT, and other observational studies [39–41, 71, 72].

Role of Patient Age and Comorbidities

The role of patient age and other comorbidities in predicting the efficacy and tolerability of bevacizumab is of particular interest given that phase III trials of first-line bevacizumab generally enrolled patients who were younger and had a better performance status than the general population with mCRC. To address this concern, several studies have analyzed the effect of age on clinical outcomes. In a pooled analysis of two placebo-controlled studies, Kabbinavar et al. [73] evaluated clinical outcomes for patients aged ≥65 years treated with first-line chemotherapy plus bevacizumab compared with chemotherapy plus placebo. The OS duration was greater in the group treated with bevacizumab (19.3 months) than in the group treated with placebo (14.3 months; HR, 0.70, p = .006). The rates of adverse events leading to study discontinuation were similar in the two groups (14.8% for bevacizumab versus 12.0% for placebo). A second retrospective analysis of pooled data from four randomized studies evaluated clinical outcomes for patients receiving chemotherapy plus bevacizumab versus chemotherapy plus placebo [74]. The HR for OS was 0.79 (95% CI, 0.66–0.93) for patients aged ≥70 years treated with bevacizumab, compared with 0.77 (95% CI, 0.69–0.86) for patients aged <65 years treated with bevacizumab. For patients who are ≥70 years old, the relative risk for an arterial thromboembolic event was ~3.2% in the control group and 6.7% in the bevacizumab group. This higher risk is proportionally the same in younger patients (i.e., approximately twofold). It should be noted that the underlying risk for an arterial thromboembolism is higher in older patients, regardless of the treatment received. The survival benefit from bevacizumab is preserved in older patients because, despite the higher risk for an arterial thromboembolic event, the major cause of mortality in older cancer patients is still cancer. Registry studies have further confirmed the safety and efficacy seen in clinical trials [75, 76]. Taken together, these data suggest that the decision of whether or not to use bevacizumab should be made based on factors other than age.

Other Biological and Chemotherapy Combinations With Bevacizumab

New combinations of chemotherapy with bevacizumab have shown encouraging results in early clinical trials. A phase II study of 5-FU, LV, oxaliplatin, and irinotecan (FOLFOXIRI) with bevacizumab in 57 patients with untreated mCRC demonstrated a PFS interval of 13.1 months (95% CI, 10.9–15.2 months), an overall RR of 77%, and a 100% disease control rate [77]. The regimen was associated with high rates of grade 3–4 neutropenia (49%) and diarrhea (14%), but there were no treatment-related deaths. The combination of bevacizumab

with FOLFOXIRI remains investigational and is currently the subject of an ongoing phase III trial [78].

Preclinical and phase II trial data suggested that combining anti-VEGF and anti–epidermal growth factor receptor (EGFR) therapies resulted in greater antitumor activity [79–81]. The phase III PACCE trial randomized patients with untreated mCRC to combination chemotherapy (FOLFOX or FOLFIRI based on physician choice) and bevacizumab, with or without panitumumab [35]. The addition of panitumumab resulted in a shorter PFS interval (10.4 months) than in the control arm (11.4 months) and a statistically significant shorter OS time (HR, 1.27; 95% CI, 1.06–1.52). Surprisingly, no differences in the OS, PFS, or RR outcomes were observed in the subset of patients with wild-type *KRAS* tumors receiving panitumumab. The CAIRO2 trial randomized patients with untreated mCRC to capecitabine, oxaliplatin, and bevacizumab with and without cetuximab [36]. The median PFS interval was shorter in the cetuximab arm (9.4 months) than in the control arm (10.7 months). In the subset of patients with wild-type *KRAS* tumors, the addition of cetuximab to chemotherapy and bevacizumab did not alter the PFS or OS outcome, but there was a trend toward a higher RR in the group receiving cetuximab (61%) than in the group receiving placebo (50%; $p = .06$). It is unclear whether the outcomes in these trials were compromised by antagonistic effects between bevacizumab and anti-EGFR monoclonal antibodies or by the greater toxicity of the combination in the setting of chemotherapy, which may have precluded the otherwise better use of all active agents.

Table 5. Summary of key biomarkers investigated in clinical trials of bevacizumab [88–93, 95, 99]

Key biomarkers evaluated
KRAS mutational status
BRAF mutational status
p53 mutational status
VEGF and *VEGFR-2* (*KDR*) gene expression
ERCC1 gene expression
VEGF A- to VEGF-D, VEGFR-1, and VEGFR-2 protein expression
CD31 expression
Neuropilin expression
Stromal thrombospondin-2 expression
Microvessel density
Plasma VEGF levels

Abbreviations: VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Biomarkers

To date, no prospectively validated biomarkers have emerged to include or exclude patients from anti-VEGF therapy. It is unknown whether interactions in the host–tumor microenvironment, biological features unique to the tumor, or features unique to the patient are most likely to yield predictors of responsiveness to treatment (Table 5) [82]. Factors mediating resistance to anti-VEGF therapy have been described in preclinical models [83, 84]. However, several markers that have appeared promising in preclinical models have failed as predictors of response in human trials [83, 85, 86]. Initial human biomarker studies evaluated the effect of the tumor–host microenvironment and tumor genotype on clinical outcomes. A retrospective analysis was performed on 278 tissue samples (bevacizumab, 153; placebo, 125) from the AVF2107g study. Stromal VEGF, stromal thrombospondin-2, and microvessel density were not predictors of a longer survival time for patients receiving bevacizumab, compared with placebo [87]. A related analysis of microdissected tumors from 295 patients enrolled in the same study demonstrated a longer OS time for all patients treated with bevacizumab, compared with placebo, regardless of their *KRAS*, *BRAF*, and *P53* mutation status [23, 88, 89]. These findings were recently confirmed in the MAX trial, in which the *KRAS* and *BRAF* mutation status failed to predict benefit with bevacizumab [90]. Post hoc exploratory analyses were performed on tumor samples from the NO16966 trial [91]. A high CD31 (higher vessel number), high VEGF-A, and low human epidermal growth factor receptor 2 expression level were correlated with a longer duration of response. High levels of neuropilin, which is a cell surface receptor for VEGF-A, VEGF, and placental growth factor, were associated with less benefit from bevacizumab.

A recent analysis demonstrated an association between intratumoral levels of VEGF-D, which can bind and activate both VEGFR-3 and VEGFR-2, and a benefit from bevacizumab. In the phase III MAX study, the expression levels of VEGF family members A through D and VEGF receptors VEGFR-1 and VEGFR-2 were analyzed using immunohistochemistry from formalin-fixed paraffin-embedded tumor tissue [92]. The expression of VEGF-D emerged as a predictor of response to bevacizumab treatment, and these results remained statistically significant after correction for baseline clinical and pathological factors. For patients treated with bevacizumab, low VEGF-D expression was predictive of a significantly longer PFS interval than with high levels of VEGF-D expression. A separate analysis suggested that VEGF-D levels increased shortly before the development of treatment resistance [93]. Interestingly, circulating VEGF-D also emerged as a predictive biomarker for bevacizumab treatment benefit in the phase III Cancer and Leukemia Group B 80303 trial of gemcitabine with and without bevacizumab for metastatic pancreatic cancer [94]. These results are considered exploratory and need confirmation in additional clinical trials.

Blood-based biomarkers have, until now, produced mixed results. A retrospective analysis of 1,816 patients with colon, lung, and renal cell cancers found that plasma VEGF levels were not predictive of a benefit from bevacizumab [95]. Interestingly, when VEGF levels from the phase III Avastin® and Docetaxel (AVADO) breast cancer trial were tested using a novel VEGF assay, an association between plasma VEGF and a benefit from bevacizumab treatment was observed [96].

Analyses using this novel VEGF assay in patients with mCRC have not yet been reported.

The role of hypertension in predicting responsiveness to bevacizumab is controversial. The most comprehensive analysis to date analyzed ~5,900 patients across six phase III studies in mCRC and breast, lung, and renal cell cancers [97]. This analysis used patient-specific data, including blood pressure values from each visit. Increased blood pressure on treatment was not predictive of treatment response to bevacizumab in five of six clinical trials. Based on these data, strategies to increase blood pressure, by increasing the bevacizumab dose or by avoiding blood pressure treatment, are likely to be of little value. Hypertension, which is a risk factor for more serious cardiovascular and cerebrovascular events, should be regularly monitored and managed.

Summary and Future Directions

Bevacizumab has demonstrated clinical benefit for the first-line treatment of patients with mCRC with a variety of fluoropyrimidine-based regimens. The choice of chemotherapy backbone in combination with bevacizumab is dependent on patient comorbidities, preferences around toxicities, and practical considerations, such as convenience and cost. For patients with a good performance status, initial therapy with bevacizumab and a combination regimen is generally preferred, with the FOLFOX, FOLFIRI, and XELOX regimens having the most data supporting their use. For patients with an impaired performance status, several studies support the benefit of initiating treatment with a fluoropyrimidine (5-FU or capecitabine) plus bevacizumab without a second cytotoxic agent.

When practical, patients should be treated to progression. Proactive symptom management and adjustments in the doses of cytotoxic agents, as well as strategically timed treatment breaks, may allow first-line treatment to become more sustainable, particularly with average treatment durations now approaching 1 year for many first-line patients. The optimal strategy for induction and maintenance therapy is not yet known; however, the results of several important trials evaluating differing maintenance approaches are due in the near future. Ongoing trials are also attempting to determine whether or not the activity of first-line therapy can be augmented even further.

Lastly, efforts to identify biomarkers related to sensitivity and resistance to bevacizumab are now reporting intriguing results. Although these efforts need independent confirmation, they are an important proof of principle for the value of these approaches. Biomarkers to guide which patients should be treated could have a substantial effect on the use of angiogenesis inhibitors for multiple tumor types. In addition, biomarkers can also be used to identify and prioritize which other factors should also be targeted. In turn, this information should greatly accelerate the development of the next generation of treatments for colorectal cancer.

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