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SYSTEMIC THERAPIES IN COLORECTAL CANCER (S.M. KAZMI, SECTION EDITOR)

Optimal Use of FOLFOXIRI Plus Bevacizumab as First-Line Systemic Treatment in Metastatic Colorectal Cancer

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Abstract

Purpose of Review Colorectal cancer is the second leading cause of cancer-related deaths in the USA with more than half of diagnosed patients developing metastatic disease. The mainstay of treatment for metastatic disease is chemotherapy, and upfront treatment has generally consisted of a two-drug chemotherapy combination (FOLFOX or FOLFIRI) plus a biologic agent. In this review, we explore the emerging role of the three-drug chemotherapy combination FOLFOXIRI plus bevacizumab as first-line treatment in metastatic colorectal cancer.

Recent Findings Randomized trials evaluating the efficacy of FOLFOXIRI plus bevacizumab have shown improvement in objective response rate, overall survival, and resection rate when compared to previous standard therapy. However, this comes with added toxicity, which can be one of the main barriers to its widespread implementation.

Summary FOLFOXIRI plus bevacizumab is an effective therapy in carefully selected patients; however, more clinical trials investigating the regimen's role in colorectal cancer remain a significant need.

Keywords FOLFOXIRI · Bevacizumab · Metastatic colorectal cancer · Conversion therapy · First-line therapy

Introduction

Colorectal cancer is the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths in the USA [1]. Approximately 50–60% of patients with colorectal cancer develop metastatic disease [2–4]. Although the mortality rate for metastatic colorectal cancer (mCRC) is high, outcomes have improved over the past several years with implementation of more targeted therapies and immunotherapy along with increased resections of oligometastasis in the appropriate patient populations [5]. In patients with unresectable metastatic disease, chemotherapy remains the mainstay of front-line therapy.

In patients appropriate for intensive therapy, treatment has largely consisted of two-drug combinations of 5-fluorouracil (plus leucovorin) and either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) plus a biologic agent (bevacizumab or an anti-EGFR monoclonal antibody). Given their similar outcomes, the choice of the initial treatment regimen is generally based on physician's preference, patient's co-morbidities, tumor mutational profile, and any prior therapies used. A triple-chemotherapy drug combination of 5-fluorouracil (5FU), oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab has recently been evaluated in the first-line setting in clinical trials and has shown promising results [6••, 7•, 8•].

Despite this, there remains some ambiguity and hesitancy in implementing this regimen into daily clinical practice. We aim to review the recent literature and shed some light on advantages and limitations of FOLFOXIRI plus bevacizumab in metastatic colorectal cancer.

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FOLFOXIRI Plus Bevacizumab as First-Line Therapy

TRIBE I Study

One of the first important trials that evaluated the use of FOLFOXIRI plus bevacizumab as initial therapy for metastatic colon cancer was the 2014 TRIBE trial by Loupakis et al. [6••].

This is a phase III randomized clinical trial that enrolled 508 patients from 34 different Italian centers with unresectable mCRC. Patients were randomized to receive treatment with FOLFOXIRI plus bevacizumab or FOLFIRI plus bevacizumab. The trial included adult patients ≤ 75 years of age with an ECOG performance status of 2 or less. The objective response rate (ORR) was 65% in the experimental group versus 53% in the control group ($P = 0.006$). The trial met its primary end point with an improvement in median progression free survival (mPFS) in the experimental arm of 12.1 months vs 9.7 months in the control arm (hazard ratio [HR] for progression = 0.75; 95% CI: 0.62–0.90; $p = 0.003$). Interestingly, the benefit in mPFS in the triplet arm was seen across all clinical and molecular subgroups except for patients who had previously received adjuvant therapy ($p = 0.04$).

Moreover, updated results after an extended median follow-up period of 48.1 months demonstrated a significant improvement in overall survival by 4 months in the FOLFOXIRI plus bevacizumab arm versus the FOLFIRI plus bevacizumab arm (29.8 months vs. 25.8 months, respectively; [HR] 0.80, 95% CI 0.65–0.98; $p = 0.03$) [7•].

CHARTA Trial

The CHARTA trial is a phase II trial of 250 patients who were randomized to standard FOLFOX plus bevacizumab versus FOLFOXIRI plus bevacizumab [9]. Adult patients ranging from 21 to 82 years of age were included, and all had an ECOG of 0–2. Results were similar to the TRIBE trial with improvement in median PFS in the triplet arm with bevacizumab compared to the FOLFOX plus bevacizumab arm (12.0 months vs 9.76 months, respectively; HR 0.77, $p = 0.61$).

The TRIBE and CHARTA trials, along with other similar phase II and phase III studies, have led to the incorporation of FOLFOXIRI plus bevacizumab into the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) consensus guidelines as a standard first-line treatment for metastatic colorectal cancer. The only recommendation for this regimen is that the patient has an excellent performance status [10–12].

Despite these recommendations and promising results, FOLFOXIRI plus bevacizumab is still not widely used. Toxicity concerns have reinforced the importance of patient selection and the need to identify which patients would benefit the most from this aggressive approach. Uncertainty about appropriate treatment options upon progression has also delayed widespread use of this regimen.

Toxicity Profile

Concerns about the tolerability of FOLFOXIRI and bevacizumab in patients in the USA may be contributing to the lack of implementation. The TRIBE data showed that FOLFOXIRI plus bevacizumab was associated with a significant increase in the rates of grade 3 or 4 neurotoxicity, stomatitis, diarrhea, and neutropenia. In the triplet arm, significantly more cycles were delayed (16.4 vs. 6.1%, $p < 0.001$), and more chemotherapy doses were reduced (21.4 vs. 8.2%, $p < 0.001$) compared with the doublet chemotherapy arm. However, there were no significant differences between the groups in the rates of febrile neutropenia, serious adverse events, or deaths due to treatment-related toxic effects [6••]. Moreover, the percentage of bevacizumab-related adverse events was consistent with the percentages in previous trials, and no significant differences between groups were reported, thus showing that chemotherapy intensification does not influence the safety profile of the anti-angiogenic agent.

On the other hand, it has been hypothesized that alternating treatment with FOLFOX plus bevacizumab and FOLFIRI plus bevacizumab (i.e., sequential FOLFOXIRI + bevacizumab) may improve the tolerability of the regimen without affecting efficacy and may help guide the choice of second-line treatment [13].

The STEAM trial, by Hurwitz et al., is a randomized 3 arm phase II trial, which included 280 patients with untreated mCRC who were randomized 1:1:1 to either concurrent FOLFOXIRI and bevacizumab (cFOLFOXIRI-BEV), sequential FOLFOXIRI with bevacizumab (sFOLFOXIRI-BEV) in which cycles of FOLFOX plus bevacizumab alternate with FOLFIRI plus bevacizumab every 4 weeks, or FOLFOX and bevacizumab [8•]. Patients were treated with 4 to 6 months of induction chemotherapy followed by maintenance therapy with 5-FU (or capecitabine, an orally delivered formulation of 5-FU) and bevacizumab. Results showed cFOLFOXIRI-BEV and sFOLFOXIRI-BEV were well-tolerated; moreover, the three-drug combinations with bevacizumab had numerically improved ORR, mPFS, and liver resection rates versus FOLFOX plus bevacizumab. In the pooled FOLFOXIRI arm, mPFS was 11.7 months versus 9.5 months in the FOLFOX with bevacizumab arm (hazard ratio, 0.7; 90% confidence interval, 0.5–0.9; $p < .01$).

No new safety concerns were observed with cFOLFOXIRI-BEV or sFOLFOXIRI-BEV in the STEAM trial, confirming the safety and feasibility of FOLFOXIRI with bevacizumab as a treatment option. The most common grade ≥ 3 treatment-related adverse events (occurring in ≥ 10% of patients) were neutropenia, hypertension, diarrhea, fatigue, hypokalemia, and anemia. Grade ≥ 3 toxicities were more common in the cFOLFOXIRI-BEV arm than in the other two arms with the exception of febrile neutropenia, constipation, and stomatitis, which were similar across all three treatment arms.

Although the incidence of some treatment emergent adverse events (e.g., grade ≥ 3 neutropenia and diarrhea) were numerically lower in the sFOLFOXIRI-BEV arm compared with cFOLFOXIRI-BEV, the incidence of grade 4 and 5 side

effects was similar, and no overall statistical difference was observed in safety between the concurrent and sequential regimens [8•].

Most of the phase II and phase III studies evaluating the triplet regimen report increased toxicity in the FOLFOXIRI arm (Table 1). However, the increase in toxicity is thought to be manageable, and careful patient selection as well as early intervention of side effects may improve tolerability [14, 15, 6••, 7•, 8•].

Patient Selection

Although the increased toxicity associated with FOLFOXIRI plus bevacizumab may preclude its widespread use, its improved efficacy over standard doublet therapy plus bevacizumab makes the regimen valuable in the appropriate patient population.

Performance Status

Several positive trials investigating the triple chemotherapy regimen have been reviewed. Overall, patients enrolled in these trials had an age range of 23 to 77 years with a median age range of 58–60 years. Most patients included in these studies had an ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1 with only a small percent of patients having an ECOG of 2 (Table 2). Excellent performance status is the only recommendation made by NCCN when considering this aggressive regimen [6••, 8•, 15••, 16, 17].

Molecular Profile

Mutational status has also been investigated to determine if there is a specific subset of patients with mCRC who may derive the most benefit from FOLFOXIRI plus bevacizumab. The TRIBE study included a similar number of patients with *KRAS* wild-type disease in both the FOLFIRI with bevacizumab (39%) arm and the FOLFOXIRI plus bevacizumab (37%) arm. The subgroup analysis showed that the treatment effect of FOLFOXIRI plus bevacizumab was independent of *KRAS* mutation status.

BRAF mutation was seen in 5.5% of patients in the TRIBE study and was found to be an adverse prognostic factor for both mPFS and OS. However, treatment effect was not significantly different between *BRAF*-wild type and *BRAF*-mutant subgroups, which suggests mutational status does not affect the regimen's efficacy [6••, 7•, 14].

A sub-analysis of the TRIBE study looking specifically at tumor sidedness along with *RAS* and *BRAF* status was done with results showing that patients with right-sided tumors achieved more relative benefit from the triplet chemotherapy plus bevacizumab with improvement in mPFS and OS. This advantage was irrespective of *RAS* and *BRAF* mutational status. [7•]

Borderline Resectable Oligometastasis

Resection of limited colorectal metastases can dramatically improve survival [10, 18]. Chemotherapy has been used to help facilitate tumor resection even in patients with non-

Table 1 Common grade ≥ 3 adverse events reported in TRIBE 1 and STEAM studies in triplet chemotherapy vs doublet chemotherapy arms

Grade ≥ 3 AE	TRIBE I [6••]		STEAM [8•]	
	FOLFIRI + Bev *n* = 254 (%)	FOLFOXIRI + Bev *n* = 250 (%)	FOLFOX + Bev *n* = 90 (%)	FOLFOXIRI + Bev *n* = 91 (%)
Neutropenia	52 (20.5)	125 (50)	32 (36)	52 (57)
Diarrhea	27 (10.6)	47 (18.8)	11 (12)	20 (22)
Nausea	8 (3.2)	7 (2.8)	5 (6)	8 (9)
Vomiting	8 (3.2)	11 (4.4)	4 (4)	6 (7)
Febrile neutropenia	16 (6.3)	22 (8.8)	3 (3)	3 (3)
Stomatitis	11 (4.3)	22 (8.8)	1 (1)	2 (2)
Peripheral neuropathy	0	13 (5.2)	6 (7)	6 (7)
VTE/Pulmonary Embolism[a]	15 (5.9)	18 (7.2)	5 (6)	7 (8)
Hypertension	6 (2.4)	13 (5.2)	14 (16)	20 (22)
Fatigue	NR	NR	5 (6)	11 (12)
Asthenia	23 (9.1)	30 (12.0)	NR	NR

Abbreviation: *Bev* bevacizumab, *AE* adverse event, *VTE* venous thromboembolism,

[a] VTE (TRIBE), pulmonary embolism (STEAM); FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; FOLFIRI, 5-fluorouracil, leucovorin, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin

Table 2 Patient characteristics, median OS, and R0 resection rates of trials evaluating FOLFOXIRI plus bevacizumab

Study	Treatment arm	Number of patients	Age range, yrs (median)	Sex (%)	ECOG (%)	Tumor sidedness (%)	Sites of metastases (%)	mOS (mo)	R0 RR (%)
TRIBE I 2014 [6••, 7•]	FOLFOXIRI + Bev	252	29–75 (60.5)	M (59.5) F (40.5)	0 (90.1) 1–2 (9.9)	Right (34.9) Left (60.3) NR (4.8)	Liver only (23.4) Other sites (76.6)	29.8	15
STEAM 2019 [8•]	cFOLFOXIRI + Bev [a]	93	23–75 (58)	M (55) F (45)	0 (67) 1 (33)	Right (46) Left (54)	Liver only (30) Other sites (70)	34	16.1
OLIVIA 2015 [15••]	FOLFOXIRI + Bev	41	32–77 (63)	M (71) F (29)	0 (56) 1 (39) 2 (5)	NR [b]	Liver only (100)	Not reached [c]	49
TRIBE 2 2020 [17]	FOLFOXIRI + Bev	339	53–67 (60)	M (53) F (47)	0 (86) 1–2 (14)	Right (38) Left [d] (62)	Liver only (31) Other sites (68) NR (< 1)	27.4	17

Abbreviation: Bev bevacizumab; *RR* resection rate; *mOS* median overall survival; *mo* months; *yrs* years; *NR* not reported; *ECOG* Eastern Cooperative Oncology Group; *FOLFOXIRI* 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; *M* male; *F* female

[a] Concurrent FOLFOXIRI plus bevacizumab in STEAM trial

[b] OLIVIA study: In the FOLFOXIRI plus bevacizumab arm, tumor site reported as colon 71%, rectum 20%, and colorectal 10%

[c] OLIVIA study: Median time to overall survival was not reached (range 0–56.0 months) in the bevacizumab–FOLFOXIRI group and was 32·2 (range 0.7–59.6) months in the bevacizumab–mFOLFOX-6 group (hazard ratio 0.35; 95% CI 0.15–0.80)

[d] TRIBE 2 study reports this as left or rectum (62%) in the FOLFOXIRI plus bevacizumab arm

resectable metastatic disease at presentation [19]. With treatment response and tumor shrinkage, tumors that were initially considered non-operable may be able to undergo curative resection.

The OLIVIA study explored the effect of FOLFOXIRI and bevacizumab on resection rates in patients with initially unresectable liver metastases from colon cancer [15••]. In this multinational phase II study, patients with unresectable liver metastases were randomized to modified FOLFOX (mFOLFOX) and bevacizumab or FOLFOXIRI and bevacizumab. The primary end point was overall resection rate. The FOLFOXIRI arm had an improved overall resection rate of 61% compared to 49% in the mFOLFOX arm (95% CI 11%–36%) with a R0 resection rate of 49% versus 23% (95% CI, 4%–48%), respectively. Median PFS was 18.6 months (95% CI 12.9–22.3) in the FOLFOXIRI arm and 11.5 months (95% CI 9.6–13.6) in the mFOLFOX arm. The incidence of grade ≥ 3 adverse events was higher in the FOLFOXIRI with bevacizumab arm compared to the mFOLFOX and bevcizumab arm, similar to what we have seen in other phase II and III studies.

In addition, a systematic review of 11 FOLFOXIRI plus bevacizumab studies showed that for unresectable liver metastatic colorectal cancer, the triplet regimen was associated with a significantly better overall response rate, leading to an almost 40% surgical conversion of liver metastases with more than one-fourth of patients having an R0 resection. [20]

These studies support that intensified chemotherapy with FOLFOXIRI and bevacizumab may play a vital role in patients with borderline liver metastases, especially with the goal of using this as conversion therapy. Long-term survival has been documented in patients who undergo complete resection of oligometastatic disease. Therefore, using the intensified triplet regimen with bevacizumab in patients with colorectal liver metastasis may even lead to a cure with tumor downsizing followed by resection [21].

High Circulating Tumor Cells

Baseline circulating tumor cell count (CTC) ≥ 3 has been defined as a poor prognostic factor. The phase III VISNU-1 trial randomly assigned 349 patients < 70 years of age with ≥ 3 circulating tumor cells to FOLFOXIRI plus bevacizumab vs FOLFOX plus bevacizumab [22]. Preliminary results presented at the 2019 annual ASCO meeting reported that initial therapy with the triple chemotherapy regimen was significantly associated with improved disease-free survival with a median of 12.4 months compared to a 9.3 months in the FOLFOX arm. Overall survival was numerically higher in the triplet arm; however, this was not statistically significant (22.3 months with FOLFOXIRI plus bevacizumab vs 17.6 months with FOLFOX plus bevacizumab). Patients in the triplet arm had significantly higher rates of grade ≥ 3

febrile neutropenia, diarrhea, and asthenia. Results of the study suggested that while patients who received FOLFOXIRI with bevacizumab did better than those who received standard therapy, having increased CTCs did not seem to independently predict response to the more aggressive treatment regimen.

Subsequent Treatment Options

Traditionally, upon progression of upfront doublet therapy (FOLFOX or FOLFIRI) plus bevacizumab, second-line therapy would consist of the doublet regimen that was not used in the first-line setting. However, if all of the most active agents are being used upfront, then the available options upon progression may be unclear. This is possibly another reason FOLFOXIRI plus bevacizumab is not used more as first-line therapy when appropriate.

The GONO group conducted the *TRIBE-2* study to address the issue pertaining to second-line treatment at progression. This phase III trial randomized patients with unresectable, treatment-naïve mCRC patients to one of two treatment arms. One treatment arm was first-line FOLFOX plus bevacizumab for 8 cycles followed by maintenance 5FU and bevacizumab, and upon progression, patients were treated with FOLFIRI plus bevacizumab. Alternatively, the other treatment arm was FOLFOXIRI plus bevacizumab for 8 cycles followed by maintenance 5FU and bevacizumab. Upon progression in this arm, full-dose FOLFOXIRI with bevacizumab was reintroduced [17].

Although this trial is ongoing, preliminary results suggest that the trial has met its primary endpoint by demonstrating that FOLFOXIRI and bevacizumab followed by the preplanned reintroduction of the same agents after disease progression provided a statistically significant improved mPFS (19.1 vs 16.4 months, HR 0.74, 95%CI 0.62–0.88, $p < 0.001$) and OS benefit (27.6 vs 22.6 months, HR: 0.81, 95%CI: 0.67–0.98, $p = 0.033$) when compared with the preplanned sequential administration of FOLFOX plus bevacizumab and then FOLFIRI plus bevacizumab upon progression [17].

The TRIBE-2 study is important in highlighting a treatment strategy upon progression for patients who receive first-line therapy with FOLFOXIRI and bevacizumab. The proposed strategy has an OS and mPFS advantage when compared to a commonly implemented treatment strategy for mCRC.

Conclusion

Multiple studies have demonstrated that FOLFOXIRI plus bevacizumab improves overall response rates, progression free survival, overall survival, and resection rates when compared to standard doublet chemotherapy regimens with bevacizumab.

Nevertheless, the FOLFOXIRI plus bevacizumab regimen has not been widely implemented for a number of reasons. Increased toxicity in a patient population with typically incurable disease likely represents the biggest drawback to this aggressive treatment. However, in patients with good performance status, toxicity can be manageable with early recognition and intervention. A review article by Loupakis et al.. suggests a practical guide for the management of grade 3 or 4 toxicities observed with FOLFOXIRI plus bevacizumab [14]. Still, the question remains if the survival benefit of about 4 months is worth the potential side effects. Another consideration is the financial burden that may arise with management of these adverse events seen in the FOLFOXIRI group (e.g., increase drug use such as granulocyte colony stimulating factor and loperamide) as well as potential increased number of office/acute care visits.

The optimal patient selection for this triplet regimen remains a challenge and warrants further investigation. Studies thus far suggest that this regimen is not appropriate for those above the age of 75 or those with a poor performance status (ECOG ≥ 2). Prior exposure to oxaliplatin in the adjuvant setting also seems to confer a poorer response. Alternatively, it may be thought that using the triplet regimen may improve outcomes in patients with aggressive disease, such as right-sided disease or *BRAF*-mutant disease; however, when it comes to tumor sidedness and molecular biomarkers, there is no clear data to suggest a specific subgroup that would benefit from the triplet chemotherapy regimen. Patients with increased circulating tumor cells in the peripheral blood, which are known to be associated with a poor prognosis, appear to benefit from FOLFOXIRI and bevacizumab compared to standard therapy; however, the response is consistent with what is typically seen in unselected patients.

The most promising clinical scenario for using FOLFOXIRI plus bevacizumab appears to be in patients with borderline resectable oligometastatic colorectal cancer. The regimen has consistently shown higher resection rates when compared to standard doublet therapy with bevacizumab, thereby offering these patients a small, yet real, chance of a cure. The risk of potential side effects with the more aggressive regimen may be worth the benefit of a possible cure.

Ultimately, further studies are needed to identify the optimal patient population that would benefit from this triplet regimen in order to maximize FOLFOXIRI plus bevacizumab use while minimizing the toxicity of this regimen in patients with metastatic colorectal cancer. As more studies investigate second-line treatment options and

comparison to regimens with anti-EGFR inhibitors, the FOLFOXIRI plus bevacizumab will hopefully find its niche in daily use.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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