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Commentary

FOLFOXIRI plus Bevacizumab Versus FOLFOX plus Panitumumab for Metastatic Left-Sided *RAS*/*BRAF* Wild-Type Colorectal Cancer: Which "Side" Are You On?

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

Abstract

This commentary focuses on the results of the study by Pietrantonio et al., which evaluated the clinical conundrum of triplet versus doublet chemotherapy in combination with targeted therapy for metastatic left-sided *RAS*/*BRAF* wild-type colorectal cancer and appears in this issue. Both FOLFOXIRI [fluorouracil, leucovorin, oxaliplatin, and irinotecan] plus bevacizumab and FOLFOX [fluorouracil, leucovorin, and oxaliplatin] plus panitumumab have shown impressive activity in this population; however, the two have not been directly compared. The article by Pietrantonio et al. presents a propensity score-adjusted analysis using information from five previous randomized trials and provides best available evidence comparing these regimens. This commentary will discuss their results and how their findings fit in current treatment paradigms. ***The Oncologist*** 2021;26:277–280

Introduction

Fluoropyrimidine-based doublet chemotherapy has remained the treatment backbone in metastatic colorectal cancer for the past 2 decades. Efforts to improve on the combination include the addition of bevacizumab or anti-epidermal growth factor receptor (EGFR) agents [1, 2] and intensification with the triplet regimen fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI), with or without targeted therapy [3–5]. The importance of tumor sidedness has emerged in recent years, and post hoc analyses demonstrate improved outcomes with anti-EGFR agents compared with bevacizumab for left-sided primaries when used with doublet chemotherapy [6]. The converse is true for right-sided tumors, with a survival advantage favoring bevacizumab [6]. For left-sided colorectal cancers that are *RAS*/*BRAF* wild type, current guidelines support first-line doublet plus anti-EGFR or triplet chemotherapy with or without bevacizumab; however, there are limited data comparing the two strategies [7].

Left-Sided *RAS*/*BRAF* Wild-Type Tumors: FOLFOXIRI + Bevacizumab Versus FOLFOX + Anti-EGFR

Pietrantonio et al. conducted a propensity-matched retrospective analysis composed of five phase II/III trials, Valentino, TRIBE, TRIBE2, STEAM, and CHARTA, comparing FOLFOXIRI + bevacizumab versus fluorouracil, leucovorin, and oxaliplatin (FOLFOX) + panitumumab in left-sided *RAS*/*BRAF* wild-type tumors [8]. This study addressed an important knowledge gap, as there are no randomized head-to-head trials specifically evaluating this question. In the analysis, no difference was observed in progression-free survival (PFS) between FOLFOX + panitumumab and FOLFOXIRI + bevacizumab (11.4 vs. 13.3 months, adjusted hazard ratio [HR] 0.82, p = .11); overall survival (OS) was also similar (30.3 vs. 33.1 months, adjusted HR 0.80, p = .14). Response rates (77% vs. 73%, adjusted OR 0.79, p = .40) and disease control rates (95% vs. 97%, adjusted OR 1.09, p = .89) were similar for FOLFOX + panitumumab and FOLFOXIRI + bevacizumab, respectively. Rates of secondary resection of metastases did not differ between the two groups. Regarding toxicity, neutropenia was more prevalent in the triplet group (48% vs. 26%, p = .03), but febrile neutropenia rates were similar (6% vs. 3%, p = .24). Considerations for choosing between the two regimens are summarized in Figure 1.

Who Is a Candidate for the Triplet Regimen?

In practice, triplet therapy is considered for fit patients with cancers exhibiting aggressive behavior and/or poor prognostic

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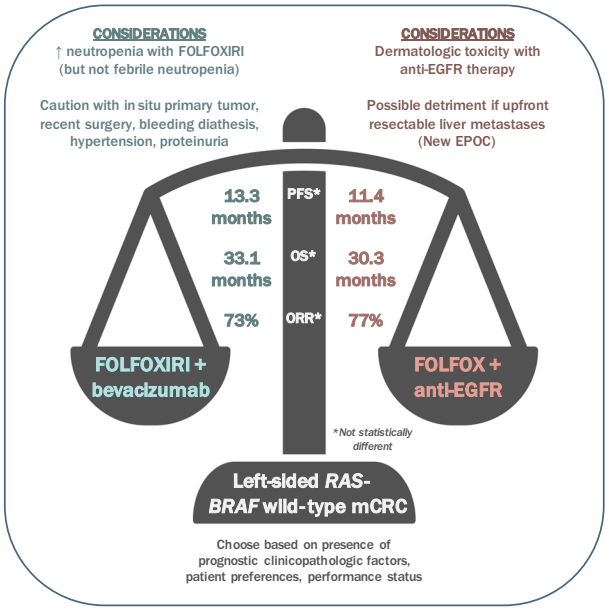

Figure 1. Considerations for choosing FOLFOXIRI + bevacizumab versus FOLFOX + anti-EGFR therapy for left-sided *RAS*/*BRAF* wild-type mCRC.
Abbreviations: EGFR, epidermal growth factor receptor; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; mCRC, metastatic colorectal cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

features. This may include tumors with *RAS* or *BRAF V600E* mutations, poorly differentiated and signet ring histology, right sidedness, and/or a high disease burden. The addition of bevacizumab is another consideration depending on *RAS*/*BRAF* mutational status, tumor sidedness, and the presence of an in situ primary tumor. A recent meta-analysis by Cremolini et al. comparing triplet-bevacizumab versus doublet-bevacizumab showed a 4.5-month OS benefit favoring the triplet group [9]. Notably, the benefit was not observed in the *BRAF V600E* subgroup (HR 1.11, 95% confidence interval 0.75–1.73) [9]. A separate meta-analysis with overlapping trials also did not find a PFS or OS benefit in *BRAF*-mutated tumors, but the OS analysis only included one trial and PFS analysis included the VOLFI study containing FOLFOXIRI + panitumumab, which may have confounded results [10].

The optimal regimen for *BRAF*-mutated tumors remains undetermined. Given the benefit of combination BRAF with or without MEK inhibitors and anti-EGFR therapy in the refractory setting [11], the phase II ANCHOR study is currently evaluating the combination of encorafenib, binimetinib, and cetuximab in the first-line setting. Preliminary data show an objective response rate of 50% and disease control rate of 85% [12]. However, there remains a role for chemotherapy in cases for which rapid treatment initiation is required and mutational status results are pending. Although there are mixed results around the use of FOLFOXIRI + bevacizumab for the first-line treatment of *BRAF V600E*-mutated colorectal cancer in the recent meta-analyses, it intuitively makes sense that one may want to use one's most aggressive option first, as these patients are prone to rapid deterioration and treatment attrition is high. A recent population-based study showed that only 26% of patients with *BRAF V600E*-mutated colorectal cancer receive second-line therapy [13].

Another setting to consider the use of FOLFOXIRI + bevacizumab combination is conversion therapy for initially unresectable liver disease, particularly in *RAS*-mutant disease. In the Pietrantonio et al. study of left-sided *RAS*/*BRAF* tumors, a benefit was not observed in secondary resection of metastases with FOLFOXIRI + bevacizumab compared with FOLFOX + panitumumab at 22% versus 18% (p = .514) [8], but the role of anti-EGFR with FOLFOX is controversial based on data from the New EPOC trial [14]. In this study of patients with upfront resectable or borderline resectable *KRAS* wild-type liver metastases, the addition of cetuximab to chemotherapy was associated with worse PFS and OS outcomes [14].

Challenges with Triplet Chemotherapy

The inclusion of additional antineoplastic agents, particularly chemotherapy, comes at a cost of additional adverse events. Clinically important adverse events are rates of neutropenia and febrile neutropenia, the latter reported to be 6% in the Pietrantonio et al. study [8]. Of note, prophylactic granulocyte colony-stimulating factor (GCSF) was not implemented in the included five studies. Clinicians will need to provide patient counseling and education around this potential complication and anticipate the need for prophylactic GCSF use. In addition, treatment intensity with triplet chemotherapy may inevitably require de-escalation of care to maintenance therapy. The phase II Valentino study in the analysis compared maintenance strategies of 5-fluorouracil-panitumumab and panitumumab alone [15], and the other studies also varied in terms of duration of induction therapy. Interpretation of the results may be impacted by these factors. In practice, the decision to switch to maintenance therapy will need to take into account an individual's tumor response, cumulative toxicity, and patient preferences.

Phase II data from the VOLFI trial supports the addition of anti-EGFR treatment to triplet chemotherapy [5], but current evidence is more robust supporting the addition of bevacizumab. However, caution must be taken with bevacizumab for patients with the following characteristics: in situ primary tumor, recent surgery, bleeding diathesis, and hypertension, which can be common scenarios for this patient population. On the other hand, anti-EGFR therapy with cetuximab or panitumumab is generally less restrictive in terms of patient selection; however, for some patients the dermatologic complications of long-term anti-EGFR therapy can be significant. This can be partially managed with prophylactic tetracycline use, topical ointments, and patient education but should not be underestimated. In fact, prophylactic use of antibiotics has been linked with improved outcomes in some studies in both colorectal and lung cancer when patients are undergoing anti-EGFR therapy [16, 17].

The overall trend in oncology is transitioning effective therapies, often in combination, from a treatment-resistant setting to an earlier line of therapy. This leaves one

wondering if we are "using up" too many lines of therapies with triplet therapy, and if it is better to prescribe drugs sequentially so we do not run out of options. However, the number of eligible patients for chemotherapy with each subsequent line of treatment declines for a variety of reasons, including declining performance status, disease progression, toxicity, and patient preference. We previously discussed how impactful this is in patients with *BRAF V600E*-mutated colorectal cancer; however, even in a molecularly unselected population attrition between first and second line can be up to 40% [18]. This may mean early use of more agents can capitalize on a window of opportunity to deliver treatment, particularly in those with poor prognostic features. Furthermore, metastatic colorectal cancer can be viewed as a treatment continuum instead of distinct lines of therapies, where there is a role for maintenance therapy, drug holidays, and incorporation of local therapies [19].

Future Directions: Unanswered Questions

The microsatellite instability high (MSI-H) population in metastatic colorectal cancer makes up ~5% of all patients, and recently pembrolizumab was shown to double PFS (16.5 vs. 8.2 months, HR 0.60, p = .0002) compared with doublet chemotherapy with or without bevacizumab or cetuximab [20]. The triplet regimen was not a comparator arm in KEYNOTE-177. A notable finding is that nearly 30% of patients had progressive disease as best overall response with pembrolizumab compared with 12% in the control arm. Further correlative studies are required to identify what differentiates progressive cases and to understand resistance mechanisms, but if we can identify those who are at risk of rapid progression, this patient population may represent a group that would benefit from a chemotherapy approach with FOLFOXIRI + bevacizumab if the patient is fit and poor prognostic features are present.

With regard to triplet chemotherapy plus anti-EGFR, phase II data from VOLFI showed the addition of panitumumab to FOLFOXIRI significantly increased the overall response rate (87% vs. 60%, OR 4.47, p = .004) in patients with *RAS* wild type [5]. We await results from PANIRINOX and TRIPLETE, which are ongoing phase II and III trials comparing FOLFIRINOX + panitumumab versus mFOLFOX6 + panitumumab in *RAS*/*BRAF* wild-type tumors [21, 22]. For now, if a triplet chemotherapy plus biologic is warranted, evidence remains more robust for FOLFIRINOX + bevacizumab.

Conclusion: No "Side" Prevails

We commend Pietrantonio et al. for undertaking this clinical question in the population of left-sided *RAS*/*BRAF* wild-type tumors, where there was a paucity of high-quality evidence. Both FOLFOXIRI + bevacizumab and FOLFOX + anti-EGFR are reasonable options, and clinicians must take patient preferences and the presence of poor prognostic clinicopathologic factors into account when choosing between the two. Further studies on the combination of FOLFOXIRI + anti-EGFR are pending and may present as another option in the near future, and correlative analyses from KEYNOTE-177 will hopefully identify how we can optimize outcomes for patients with MSI-H colorectal cancer that progress rapidly on first-line immunotherapy, and this is a population where further efforts to improve outcomes are needed.

Disclosures

The authors indicated no financial relationships.

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Editor's Note:
See the related article, "FOLFOXIRI-Bevacizumab or FOLFOX-Panitumumab in Patients with Left-Sided RAS/BRAF Wild-Type Metastatic Colorectal Cancer: A Propensity Score-Based Analysis," by Filippo Pietrantonio, Giovanni Fucà, Daniele Rossini et al., on page 302 of this issue.