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Challenging Cases

Continuing Single-Agent Bevacizumab as Maintenance Therapy After Induction XELOX (or FOLFOX) Plus Bevacizumab in First-Line Treatment of Metastatic Colorectal Cancer

SECTION EDITOR'S NOTE:

Metastatic colorectal cancer is the second leading cause of cancer death in the United States. Since 1995, treatment regimens have included capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, aflibercept, and reforafenib. These medications have doubled the median survival of patients and improved the 5-year survival from less than 1% to 20%. Approximately 75% of patients stop first-line chemotherapy in clinical trials for reasons other than progressive disease and face the question of whether to consider "maintenance" chemotherapy or take a chemotherapy break. In this challenging case, Drs. Díaz-Rubio, Pietrantonio, and de Braud reflect on the data and offer their opinions. If each of the nearly 40,000 patients in the U.S. who face this decision chooses bevacizumab, the total cost is approximately $240 million per dose ($6,000 per infusion). The importance of this question and the cost to society are enormous.

PRO

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The question of whether to continue bevacizumab after completing induction therapy is currently a challenge for oncologists. The optimal duration of chemotherapy in patients with unresectable metastatic colorectal cancer (mCRC) is critical because treatment duration directly influences quality of life, toxicity, cost, and potentially patient survival. An attractive but not very well validated approach extensively used by oncologists is to either administer induction chemotherapy (3–6 months of treatment) followed by discontinuation until disease progression or administer standard chemotherapy with treatment-free "holidays." These strategies are only acceptable if progression-free survival (PFS) and overall survival (OS) are not compromised. It is essential to remember that chemotherapy in patients with unresectable mCRC is palliative and to consider the potential toxicity of treatment, which may in some cases be cumulative. In patients with unresectable mCRC, the most effective strategy is a continuum of care employing several active drugs over different lines of therapy; however, consideration, prevention, and management of toxicities are fundamental to this approach.

Many trials have aimed to answer the question of optimal chemotherapy duration for mCRC in the palliative setting. The most popular strategy has been to administer induction chemotherapy for several months followed by chemotherapy-free in-

CON

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The clinical experience suggests that maintenance treatment with bevacizumab alone can be of value only in a limited subset of patients with advanced colorectal cancer who can achieve long-term disease control by prolonged inhibition of angiogenesis. In the first-line setting, the median progression-free survival (PFS) time of 9.4 months reported by Saltz et al and 10.6 months reported by Hurwitz et al [1–2] indicate the need for active second-line treatment soon after bevacizumab-based chemotherapy.

Filippo de Braud

Several maintenance strategies, such as low-dose/single-agent fluoropyrimidines and targeted therapies, are under clinical evaluation with the aim of prolonging the initial clinical benefit, without jeopardizing quality of life. This issue was initially addressed by the OPTIMOX1 trial [3], which demonstrated that early discontinuation of oxaliplatin and prolonged maintenance based on fluoropyrimidines alone were not detrimental in terms of PFS, with significantly less cumulative toxicities.

Although bevacizumab has little or no activity as single-

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tervals for some or all of the agents. The three approaches that have been investigated are "stop-and-go" chemotherapy, restarting on progression; "on-off" chemotherapy, in which chemotherapy is intermittent or agents are alternated; and maintenance chemotherapy, in which some but not all of the components are stopped after induction.

Three studies have analyzed the stop-and-go strategy. The findings of a 2003 Medical Research Council (MRC) trial provided no clear evidence of benefit for continuing therapy indefinitely until disease progression [1], whereas the OPTIMOX2 study concluded that complete discontinuation of chemotherapy had a negative impact compared with maintenance therapy [2]. In another MRC study, a priori specified noninferiority of intermittent chemotherapy versus continuous treatment was not proven, although this approach was valid for some patients [3]. In a study from the Italian Group for the Study of Gastrointestinal Cancer of the intermittent or alternating on-off strategy, similar efficacy was observed for continuous versus intermittent treatment [4].

The concept of maintenance therapy—that is, stopping some but not all agents—has also been evaluated. In the OPTIMOX1 study, patients received leucovorin, fluorouracil, and oxaliplatin (FOLFOX4) until disease progression or FOLFOX7 for 3 months followed by maintenance without oxaliplatin for 6 months and then reintroduction of oxaliplatin [5]. Three months of treatment with FOLFOX7 was as efficacious as 6 months of treatment with FOLFOX4 and the incidence of grade 3 and 4 events during the oxaliplatin-free period favored FOLFOX7 [5].

Two studies have evaluated the role of bevacizumab as maintenance therapy. The CONcePT trial compared intermittent versus continuous oxaliplatin, as part of the FOLFOX regimen, combined with bevacizumab; results showed that PFS was inferior with continuous administration [6]. The MACRO TTD trial from the Spanish Cooperative Group for the Treatment of Digestive Tumors was a multicenter, randomized, phase III study evaluating the efficacy and tolerability of 6 cycles of bevacizumab plus capecitabine plus oxaliplatin (XELOX) followed by maintenance with either XELOX-bevacizumab or single-agent bevacizumab [7]. There were no statistically significant differences in overall response rate or PFS between the two arms, although there was a nonsignificant trend toward inferior overall survival with single-agent bevacizumab maintenance. This study suggests that maintenance bevacizumab after induction of XELOX-bevacizumab might be an appropriate option in patients with mCRC.

In addition to its potential role as a maintenance strategy, bevacizumab may also be active after disease progression. The observational BRITE study suggests an advantage in overall survival for continuing bevacizumab beyond progression [8]. The benefit of continuing bevacizumab after progression has been also observed in the recent TML study [9]. More evidence for the benefit of continuing antiangiogenic therapy after disease progression is emerging from the ongoing VELOUR study (with aflibercept) [10] and CORRECT study (regorafenib) [11], which both suggest the value of this approach.

In conclusion, several studies indicate that maintenance therapy with bevacizumab is a reasonable approach when the patient has obtained the maximal response after 4–6 cycles of induction chemotherapy. Regarding whether to use maintenance single-agent bevacizumab following induction XELOX agent for refractory disease, there is a strong rationale for synergistic combination with effective chemotherapy: the therapeutic blockade of vascular endothelial growth factor induces complex changes in the context of the stromal compartment of tumor lesions, such as reorganization of blood vessels, vasculature pruning, and reduction of interstitial fluid pressure, allowing a better intratumoral delivery of chemotherapeutic drugs [4]. Therefore, initial registration trials of bevacizumab in combination with first-line chemotherapy were designed to continued the whole treatment until disease progression [1, 2]. However, the compliance to prolonged chemotherapy was limited, so chemotherapy-free intervals or deintensified maintenance treatments may be well-accepted strategies.

The trial by Díaz-Rubio et al. [5] investigated the optimal maintenance treatment of metastatic colorectal cancer after 6 cycles of capecitabine plus oxaliplatin (XELOX) plus bevacizumab, with either bevacizumab alone or the same first-line regimen until disease progression. Although the MACRO TTD study did not meet the prespecified statistical criteria for noninferiority of maintenance bevacizumab alone, the detrimental effect in terms of PFS was not clinically relevant (9.7 versus 10.4 months; hazard ratio: 1.10; 95% confidence interval: 0.89–1.35), and it might have been outweighed by the improvement of quality of life. However, evidence-based medicine has emerged as our new paradigm to prevent inappropriate variations in the clinical practice; thus, it must be pointed out that the MACRO TTD trial was not designed to look into the role of maintenance bevacizumab, but mainly the effect of stopping or continuing doublet chemotherapy after a prespecified number of cycles. Moreover, the noninferiority design of the MACRO TTD study could be justified only if the experimental strategy (i.e., maintenance bevacizumab) was previously demonstrated superior over placebo or at least equivalent to an active comparator (i.e., maintenance fluoropyrimidines).

We emphasize that the role of maintenance bevacizumab should be investigated by a randomized trial planning observation alone as control group after the induction phase. Currently, the CAIRO3 trial is addressing the role of maintenance with metronomic capecitabine and bevacizumab versus observation; this is a very promising strategy to obtain a potent blockade of angiogenesis, with the consequent significant outcome improvement using a well-tolerated and multitargeted antiangiogenic maintenance therapy [6]. Nevertheless, this trial does not address the role of chemotherapy-free maintenance treatment with bevacizumab alone. More pragmatically, the Arbeitsgemeinschaft Internistische Onkologie ML21768 study has the purpose to identify the optimal maintenance strategy through randomization among fluoropyrimidine and bevacizumab, bevacizumab alone, and no active treatment. However, the primary endpoint of time-to-treatment-failure could be biased by the significant rate of dropout usually reported in previous colorectal cancer trials investigating stop-and-go and maintenance strategies.

The current data support the continuation of chemotherapy or bevacizumab in combination with chemotherapy (mainly based on fluoropyrimidines alone due to oxalipla-

(or FOLFOX) plus bevacizumab in the first-line setting, a definitive answer is likely to come from ongoing trials evaluating maintenance bevacizumab after standard chemotherapy in the DREAM, CAIRO-3, and AIO-ML21768 [12] studies. Each of these will be important in determining how best to optimize efficacy and minimize side effects in this patient population, particularly as they include quality-of-life assessments that will help quantify the benefits for patients of more intensive versus less intensive maintenance regimens.

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tin-related cumulative toxicity) until progressive disease or unacceptable toxicity. In fact, after an initial period of combination chemotherapy, maintenance treatment based on single-agent fluoropyrimidines prolongs PFS if compared with an early and complete treatment break [3, 7–8]. Recently, a phase II randomized trial of maintenance enzastaurin/placebo with 5-fluorouracil, leucovorin, and bevacizumab after 3 months of bevacizumab-based doublet chemotherapy reported a promising PFS time of 11.3 months in the placebo arm [9].

No data are currently available on the role of maintenance with bevacizumab alone as compared to either chemotherapy or placebo. Current and future trials are contributing to focus on the knowledge of antiangiogenic treatment of metastatic colorectal cancer, although active and potentially cost-saving research is warranted to validate predictive biomarkers [10].

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