

New active drugs for the treatment of advanced colorectal cancer

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Abstract

Newer active drugs have been recently added to the pharmacological armamentarium for the treatment of metastatic colorectal cancer. Aflibercept, a recombinant fusion protein composed of the extracellular domains of human vascular endothelial growth factor receptors (VEGFR) 1 and 2 and the Fc portion of human immunoglobulin G1 (IgG1), is an attractive second-line option in combination with folfox for patients who have failed folfox +/- bevacizumab. Ramucirumab, a human IgG1

monoclonal antibody that targets VEGFR-2, provided similar results in the same setting. Tas-102, an oral fluoropyrimidine, and regorafenib, a multi-tyrosine kinase inhibitor, are both able to control the disease in a considerable proportion of patients when all other available treatments have failed. These new therapeutic options along with the emerging concept that previous therapies may also be reintroduced or rechallenged after regorafenib and Tas-102 failure are bringing new hope for thousands of patients and their families.

Key words: Colorectal cancer; Aflibercept; Ramucirumab; Tas-102; Regorafenib

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Core tip: A brief review dealing with four new active drugs for the treatment of metastatic colorectal cancer covering also the very recent publication of the Tas-102 trial on *New England Journal of Medicine*.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of tumor and represents 8% of all tumors in men and women. CRC is the third leading cause of death in occidental states^[1].

Earlier diagnosis and improved treatments have reduced mortality rate in CRC, but the overall survival (OS) of patients affected by metastatic CRC (mCRC) remains low.

Since 2000, the only useful agent for the treatment of mCRC was 5-fluorouracil. Subsequently, irinotecan

(1996), capecitabine (1998) and oxaliplatin (2002) were introduced, but the most important advancement in the treatment of mCRC was the introduction of targeted therapies such as bevacizumab (2004), cetuximab (2004) and panitumumab (2006).

The selection of first-line therapy remains challenging because the choice of subsequent lines of therapy is dependent on the first administered treatment. Until a few years ago, the only biological therapy that was used as a second-line treatment was bevacizumab, whose target is vascular endothelial growth factor (VEGF)-A. New efficient agents for mCRC treatment have recently been identified; the most promising of these agents are aflibercept, regorafenib, tas-102 and ramucirumab. Aflibercept and ramucirumab are antivasular agents that are useful in second-line treatment settings; tas-102 is a chemotherapeutic agent, and regorafenib acts as multi-tyrosine kinase inhibitor.

Based on the results of the VELOUR study, aflibercept has entered clinical practice. This drug has a wider spectrum of action than bevacizumab and is effective and well-tolerated.

Aflibercept is a recombinant fusion protein composed of the extracellular domains of human VEGF receptors (VEGFR) 1 and 2 and the Fc portion of human immunoglobulin G1 (IgG1). Aflibercept interferes with the growth of tumors *via* inhibition of vascularization by binding VEGF-A and VEGF-B to prevent their interaction with VEGFR. Moreover, aflibercept can bind with high affinity to placental growth factor (PIGF) to enhance the inhibition of VEGFR^[2].

Aflibercept has been evaluated both as a first-line and second-line treatments for mCRC and in second-line settings. In phase 2, randomized, noncomparative, open-label study of aflibercept and modified Folfx6 for the first-line treatment of metastatic colorectal cancer (AFFIRM), aflibercept failed to produce a significant difference in progression-free survival (PFS)^[3]. By contrast, the double-blind phase III VELOUR trial demonstrated that aflibercept plus FOLFIRI as a second-line treatment significantly improved OS (13.5 mo vs 12.06 mo; HR = 0.817, $P = 0.0032$), PFS (6.9 mo vs 4.67 mo; HR = 0.758, $P < 0.0001$) and response rate (RR) (19.8% vs 11.1%) compared with placebo plus FOLFIRI. Of the patients enrolled in this study, 30.4% received bevacizumab as first-line treatment, but this treatment was not associated with decreased clinical benefits^[4], most likely due to the different mechanism of action of aflibercept. Indeed, some authors have suggested that aflibercept can resensitize patients to antiangiogenic treatments by inhibiting PIGF^[5].

The most recently evaluated antivasular drug is ramucirumab, a human IgG1 monoclonal antibody that targets VEGFR-2 and for which good results have been observed in the treatment of gastric cancer^[6]. In the RAISE study, ramucirumab plus FOLFIRI was administered as a second-line treatment in patients affected by mCRC who had been pretreated with bevacizumab. Improvements in both OS (13.3 mo vs

11.7 mo) and PFS (5.7 mo vs 4.5 mo) were observed, consistent with the findings of other trials of the use of antiangiogenic drugs after first-line treatments. In the ramucirumab arm, increases in the frequencies of neutropenia (28% grade 3 vs 15% in the placebo group) and hypertension (11% grade 3 vs 3%) were observed but not grade 3 bleeding or gastrointestinal hemorrhage^[7].

Despite the differences in the design of these two studies, similar survival results were obtained. Because there are no substantial differences in their efficacies and tolerabilities and no predictive biomarkers are available, the choice between these antivasular agents will be quite difficult.

Decisions related to third-line therapies and beyond are less difficult. Relevant research efforts have identified two new drugs, regorafenib and TAS-102.

Regorafenib is a multikinase inhibitor that acts on angiogenesis *via* VEGFR1-3 and TIE2, on the micro-environment through PDGFR- β and FGFR and on cellular proliferation *via* c-KIT, PDGFR, c-RET, B-RAF, and C-RAF^[8]. Two important trials of the use of regorafenib for mCRC have been conducted, the CORRECT and CONCUR trials^[8,9]. The first trial was a multicenter, randomized, double-blind, placebo-controlled, phase III study that enrolled 720 patients with mCRC. They had been heavily pretreated and received 160 mg of regorafenib daily for 3 wk on, 1 wk off plus the best supportive care (BSC) or placebo plus BSC on the same schedule. This trial involved 16 countries and 114 centers. The second trial was a smaller trial that enrolled 200 pretreated Asian patients who were randomized 2:1 to regorafenib or placebo, respectively.

Despite the differences in these studies, both reported increases in OS (HR = 0.77, 95%CI: 0.64-0.94 vs HR = 0.55, 95%CI: 0.395-0.765) and PFS (HR = 0.49, 95%CI: 0.42-0.58 vs HR = 0.311, 95%CI: 0.222-0.435) due to regorafenib. The substantial difference between the results of these trials was probably due to differences in the sample sizes, the number of lines of therapy administered prior to regorafenib and the ethnicities of the enrolled patients. Nearly half of the patients who participated in the CORRECT trial had received at least four lines of chemotherapy, compared to only 38% of the CONCUR patients. The median treatment durations were 7.3 wk in the first trial and 10.6 wk in the second, supporting the hypothesis that the better outcomes reported in the CONCUR trial were due to less pretreatment. The capacity of regorafenib to resensitize cells to subsequent treatments has also been investigated. Twenty-six percent of the patients in the CORRECT trial underwent another therapy after regorafenib. Additional evidence regarding such situations is needed^[8].

Although both studies demonstrated that regorafenib is effective independent of RAS and B-RAF status when used as monotherapy, predictive factors for the treatment response have not been identified. The roles of ECOG PS (*i.e.*, 0 vs 1), lactic dehydrogenase,

neutrophil to lymphocyte ratio, platelet count, the rs2010963 SNP of VEGF-A, ANG-2, interleukin-6 (IL-6), IL-8, PIGF, sTie-1, sVEGFR-1, VEGF-A, VEGF-C, VEGF-D, VEGF-A-121, BMP-7, M-CSF, SDF-1, TIMP-2, and VWF have been investigated but have not yielded definitive results^[10,11]. The reported toxicities of regorafenib are acceptable and primarily include hand and foot skin reactions, fatigue, diarrhea, hypertension and rashes. Based on the promising results of the CORRECT and CONCUR trials, regorafenib is entering clinical practice.

In addition to molecularly targeted drugs, new chemotherapeutic drugs with "more traditional antitumor activity", such as the new antitumor nucleoside TAS-102, continue to be developed. TAS-102 is a combination of a thymidine-based nucleic acid analogue, trifluridine (FTD), and tipiracil hydrochloride, and the latest of which is a thymidine phosphorylase inhibitor. FTD is a thymidylate synthase inhibitor^[12-14]. FTD also appears to be incorporated into DNA, thereby providing a second mechanism of antitumor activity^[15,16]. The differences in the mechanisms of action of FTD and fluoropyrimidines are supported by the results of preclinical studies indicating that TAS-102 is active and significantly more effective than 5-FU against human cancer cell sublines that are resistant to 5-FU^[17,18]. A double-blind, randomized (2:1), placebo-controlled, phase II study of TAS-102 (given twice daily for 5 d per week with 2 d of rest over 2 wk, repeated every 4 wk) enrolled 169 Japanese patients with mCRC refractory to chemotherapeutic regimens, including fluoropyrimidine, oxaliplatin and irinotecan^[19]. Only one major response was observed in the TAS-102 group, but the disease control rate (DCR; partial response + stable disease) was 43.8% vs 10.5% in the placebo group ($P < 0.0001$). PFS (based on independent reader assessments) was 2.0 mo in the TAS-102 group and 1.0 mo in the placebo group (HR = 0.41, $P < 0.0001$). The median OS was 9.0 mo in the experimental group and 6.6 mo in the placebo group (HR = 0.56, $P = 0.001$). The safety profile of TAS-102 was favorable; no treatment-related deaths were observed, and grade 3 or 4 neutropenia was the most frequently reported toxicity ($\geq 50\%$ of patients). Based on these results, the Refractory Colorectal Cancer Study (RECOURSE) was performed. The RECOURSE was a multicenter, randomized, double-blind, phase III trial in which 800 patients with mCRC refractory or intolerant to all previous chemotherapy regimens available in the setting were randomly (at a 2:1 ratio) assigned to receive TAS-102 (35 mg/m² per dose twice daily) or placebo. The results of this study were recently published^[20] and it indicated that median PFS was 2.0 mo in the TAS-102 arm vs 1.7 mo in the placebo (HR = 0.48, $P < 0.0001$). The objective RRs were 1.6% and 0.4% ($P = 0.286$) in the TAS-102 arm and the placebo arm, respectively. Furthermore, the DCRs were 44% and 16% ($P < 0.0001$) in the treatment and placebo arms, respectively, and the median OS was increased in the TAS-102 arm (7.1 mo vs 5.3 mo; HR = 0.68, 95%CI: 0.58-0.81; $P < 0.0001$). The benefit of TAS-102 in terms

of OS was observed in all of the pre-specified subgroups which included the following three stratification factors: Time from the first diagnosis of metastases to randomization, KRAS status and geographical region. The benefit of TAS-102 treatment after adjustments for the three prognostic factors (time since diagnosis of the first metastasis, ECOG performance status, and the number of metastatic sites) was maintained in a multivariate Cox regression analysis (HR = 0.69, 95%CI: 0.58-0.81). The promising results of this study confirm the role of TAS-102 in the treatment of mCRC patients who are resistant, refractory or intolerant to all standard available therapies.

In conclusion, the second-line setting has been enriched by two new drugs, aflibercept and ramucirumab, with similar efficacies and tolerabilities, but the correct strategy for the use of these drugs is unknown, and no predictive factors have been identified. The landscape for more advanced lines of therapy with regorafenib and TAS102 is also broadening. Our pharmacological armamentarium against metastatic colorectal cancer is becoming richer and smarter each day. Stay tuned for the next exciting news!

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