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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Which strategy after first-line therapy in advanced colorectal cancer?

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Abstract

Second-line therapy for advanced colorectal cancer is an integral part of the treatment strategy that needs to be set from the beginning for each patient, bearing in mind the expected toxicities of chosen treatments, the patient's clinical condition, comorbidities, preferences, the aims of the treatment and the molecular status. Furthermore, the distinction between lines of therapy is no longer absolute. The perspective of "continuum of care" includes switching chemotherapy prior to disease progression, maintenance therapy, drug "holidays" if needed, surgical resection of metastases in selected patients, and seems to allow a tailored treatment, in which patients are more likely to benefit from exposure to all active agents, which is known to correlate with overall survival. The scenario of second-line treatment has changed dramatically over the years and could currently benefit from several options including chemotherapy with a single agent or in combination and the addition of molecular-targeted agents developed in the last decade, such as epidermal growth factor receptor antibodies (cetuximab, panitumumab) and vascular endothelial growth factor-targeting agents (bevacizumab, aflibercept), with the possibility of bevacizumab use even beyond first progression. The purpose of this review is to summarize the most important scientific data supporting the use of chemotherapy and the new biologic agents in the second-line setting in advanced colorectal cancer.

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Key words: Advanced colorectal cancer; Second-line; Targeted agents; Polychemotherapy; Overall survival

Core tip: This is a review of the current literature on second-line options in advanced colorectal cancer. This review was performed to analyse the different possible choices in this setting and the best strategies to treat patients with all available active drugs.

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INTRODUCTION

Second-line therapy is an integral part of the treatment strategy for advanced colorectal cancer (aCRC). The availability of all active agents has been beneficial in patients with this disease, with an overall survival (OS) rate directly correlated to the number of agents the patients are exposed to[1]. Recently, the introduction of agents targeting the angiogenic and epidermal growth factor receptor (EGFR) pathways, including bevacizumab, aflibercept, regorafenib, cetuximab and panitumumab,

have expanded treatment options, particularly for pretreated diseases and upfront treatment[2-8]. The correct course of treatment, from the first-line to later lines of treatment, has yet to be validated, but the prudent application of all active drugs in the treatment strategy should be designed for each patient with advanced CRC. The strategy should be modified according to the site of disease, endpoint of cure, age, performance status and comorbidities.

Treatment options in pretreated patients depend on different parameters. First, the choice of second-line therapy is linked to the first-line agents the patients have been exposed to. If irinotecan was the agent of choice (*e.g.* FOLEIRI alone or in combination), oxaliplatin + 5-fluorouracil (*e.g.* FOLFOX) will be the cornerstone of treatment for the second-line.

Toxicity parameters, patient condition and preferences are alternative modes of choosing treatments. In the presence of disseminated disease, in poor performance status patients, and where palliation of symptoms and prolongation of progression-free survival (PFS) are the main endpoints, a sequence of single agents is a concrete alternative to second-line poly-chemotherapy. Two trials addressed this issue: the FOCUS and CAIRO trials. In both trials, the OS was similar in both study groups (upfront and second-line combinations *vs* single agents in both the first- and second-lines). However, in both studies, the median OS in the single agent groups was lower than expected (13.9 and 16.3 mo, respectively) with the modern agents now available. Conversely, a more intensive schedule, including biologic agents, has shown a benefit when adopted in combination with standard doublets. For example, the addition of panitumumab and aflibercept to FOLFIRI improved the outcomes in the oxaliplatin-pretreated population[3,7]. In second- or further lines of treatment, the influence of subsequent therapies is less pronounced; therefore, an OS benefit is more likely to be demonstrated. This is the reason why first-line agents confer little or nonsignificant gains in median OS. In this trial, the post-progression survival, that is the survival after first progression until death, has an enormous influence on the OS with first-line treatment[9]. This confirms that second-lines and beyond have increasing relevance on the overall treatment strategy.

With the current state-of-the-art CRC treatments, the advent of new agents, and the different treatment options that are now available, we have performed a review of the current literature to discuss the different options for patients with metastatic CRC who have failed first-line treatment.

SECOND-LINE TREATMENT: CHOICE OF CHEMOTHERAPY

The treatment strategy in advanced colorectal cancer has changed over the years, due (especially) to the availability of several new drugs which are able to double the average median survival rate, compared to the era in which 5-fluorouracil (5-FU) was the only active agent. Furthermore, the model of distinct lines of chemotherapy, in which regimens containing non cross-resistant drugs are used in progressive disease, is debated. A continuum of care approach has been proposed, and seems to allow a more tailored treatment. This approach includes switching chemotherapy prior to disease progression, maintenance therapy, drug holidays, and surgical resection of metastases in selected patients. With this approach, the distinction between lines of therapy is no longer absolute. This model emphasizes the importance of an individualized treatment strategy in aCRC, in which patients are given the opportunity to benefit from exposure to all active agents that correlate with OS[10].

Regardless of age, patients with a poor performance status (PS) (*e.g.* Eastern Cooperative Oncology Group PS $\geqslant$ 2 or Karnofsky PS $<$ 60) usually tolerate chemotherapy poorly and have a poor short-term prognosis.

Some patients, especially those whose PS decline is not cancer related, will be treated with monotherapy, often with LV-modulated 5-FU or capecitabine.

As a single agent, irinotecan has shown clinical benefits after 5-FU failure in patients with aCRC. In a randomized trial, 279 patients with 5-FU-refractory disease were randomly assigned, with a 2:1 ratio, to irinotecan with best supportive care (BSC) (189 patients) or to BSC alone (90 patients)[11]. The OS rate was significantly better in the irinotecan group (P = 0.0001), with a 1-year survival of 36.2% *vs* 13.8% in the BSC group. The quality-of-life analysis (except the diarrhoea score) also favoured irinotecan.

Conversely, oxaliplatin alone in the second-line setting has shown a low level of activity. In a randomized phase Ⅲ trial, 423 patients with metastatic colorectal cancer who progressed after IFL (irinotecan, fluorouracil, and leucovorin) therapy were randomly assigned to bolus and infusional FU and leucovorin (LV5FU2), single-agent oxaliplatin, or the combination (FOLFOX4). FOLFOX4 proved to be superior to LV5FU2 in all measures of clinical efficacy (objective response rate, time to tumour progression, and alleviation of tumour-related symptoms); however, single-agent oxaliplatin was not superior to LV5FU2 in any measure of efficacy, with an objective response rate of 0%[12].

The sequential use of active single agents, rather than combination regimens, has been proposed to reduce the overall toxicity of therapy, maintaining the same outcome in terms of survival.

The European FOCUS and CAIRO trials addressed the issue of initial combination *vs* single agent therapy.

In the FOCUS trial, 2135 non-pretreated patients were randomly assigned to three treatment strategies in the ratio of 1:1:1. Strategy A was single-agent fluorouracil until failure, then single-agent irinotecan. Strategy B was fluorouracil until failure, then combination chemotherapy (FOLFOX or FOLFIRI). Strategy C was upfront combination therapy. The OS (primary endpoint) of the patients allocated to Strategy A was 13.9 mo. The

median survival for each of the other groups was longer (15 mo for Strategy B, 16.4 mo for Strategy C). Only the comparison of initial FOLFIRI *vs* sequential single agent therapy was statistically significant (median survival: 16.7 *vs* 13.9 mo). This trial showed that sequential single agent therapy did not compromise overall survival, and initial single-agent treatment upgraded to combination when required was not worse than the first-line combination, and could be an option to consider.

The trial allowed the use of FOLFOX or FOLFIRI as the third-line treatment, but only 23% of all patients received all three active agents, with a higher rate for patients allocated to Strategy C than for Strategy A (33% *vs* 16%)[13].

In the CAIRO trial, 820 patients with aCRC were randomized to receive either first-line treatment with capecitabine, second-line irinotecan, or third-line capecitabine plus oxaliplatin (sequential treatment; n = 410), or first-line treatment with capecitabine plus irinotecan and second-line treatment with capecitabine plus oxaliplatin (combination treatment; n = 410). The median OS (primary endpoint) was similar for the sequential *vs* initial combination therapy (16.3 *vs* 17.4 mo) and PFS was superior with combination therapy. The XELIRI regimen was affected by a higher rate of grade 3-4 diarrhoea, and almost half of the patients starting with this combination did not receive second-line chemotherapy[14].

As in the FOCUS trial, in the CAIRO study the proportion of patients treated with a sequential strategy who eventually received all three drugs (19% in FOCUS and 36% in CAIRO) was lower when compared with patients treated with a combination regimen (33% in FOCUS and 55% in CAIRO). These data support the hypothesis that patients receiving first-line combination therapy are more likely to receive all three active agents during the course of their disease than those who initiate treatment with a single agent[15].

Thus, in fit patients, a reasonable first-line with a combination doublet (FOLFOX, XELOX, or FOLFIRI), and the choice of chemotherapy regimen, will be driven by the expected toxicity profile and by the patient' s preference. The second-line treatment should be linked with the first-line choice, and FOLFIRI (or irinotecan alone) will follow a first-line with an oxaliplatin-based regimen. Conversely, it seems logical to use FOLFOX in the second-line treatment if the irinotecan-based regimen has been previously chosen.

Anti-EGFR in the second-line setting

Cetuximab is a mouse/human chimeric monoclonal antibody, which binds the EGFR, competitively inhibiting ligand binding, and inducing receptor dimerization and internalization. In combination with irinotecan, after first-line fluoropyrimidine and oxaliplatin treatment failure, it was shown to improve the PFS and response rates in the multicentre, open-label, phase Ⅲ EPIC trial. In this study, 1298 patients, previously treated during first-line therapy with a fluoropyrimidine and oxaliplatin, were randomly assigned to cetuximab plus irinotecan, or irinotecan alone. The median OS (primary endpoint) was similar between the two arms of the study: 10.7 mo (95%CI: 9.6-11.3) with cetuximab/irinotecan and 10.0 mo (95%CI: 9.1-11.3) with irinotecan alone (HR = 0.975; 95%CI: 0.854-1.114; P = 0.71).

However, cetuximab combined with irinotecan significantly improved the PFS (median, 4.0 *vs* 2.6 mo; HR = 0.692; 95%CI: 0.617-0.776; $P \leqslant 0.0001$) and RR (16.4% *vs* 4.2%; $P < 0.0001$), and was associated with better scores in the QOL analysis of global health status (P = 0.047). The lack of difference in terms of survival could be explained by the fact that almost 47% of the patients assigned to irinotecan eventually received cetuximab. The addition of cetuximab to irinotecan did not result in meaningful increases in toxicity, with the exception of acneiform rash, diarrhoea, and electrolyte imbalances[16].

The KRAS mutation status was retrospectively obtained in only 23% of the randomized patients. In the small subset of patients with wild-type KRAS tumours (15% of the whole population), the PFS was longer when cetuximab was added to irinotecan, but the RR and OS were similar[17].

The activity of cetuximab + chemotherapy has been reported in a pooled analysis by Barni *et al*[18], which included 1712 KRAS wild-type patients. The overall response rate was 31.9%, with similar response rates of 28.7% for the second-line treatment and 31.1% for the third- or further lines. The overall weighted median OS and PFS were 12.5 and 6 mo, with a weighted OS of 11.56 and 12.2 mo for the second- and further line CRC settings, respectively.

Panitumumab is a fully human monoclonal antibody directed against the EGFR gene. As a single agent, it has been shown to prolong PFS in patients who had progressed after standard chemotherapy (5-FU, irinotecan and oxaliplatin)[2].

In the second-line setting, the efficacy of the combination panitumumab-FOLFIRI was evaluated in a phase Ⅲ trial, in which 1186 patients were randomly assigned to receive panitumumab plus FOLFIRI, *vs* FOLFIRI alone. The patient subgroups on the basis of KRAS status were considered. In the wild-type KRAS subpopulation, the combination FOLFIRI-panitumumab resulted in a significant improvement in PFS (5.9 mo for panitumumab-FOLFIRI *vs* 3.9 mo for FOLFIRI, HR = 0.73; 95%CI: 0.59-0.90; P = 0.004). A non-significant trend toward increased OS was observed, and the median OS was 14.5 mo *vs* 12.5 mo, respectively (HR = 0.85, 95%CI: 0.70-1.04; P = 0.12). One acceptable hypothesis to explain the discrepancy between the PFS and OS is crossover in the chemotherapy alone study groups. The response rate was improved from 10% to 35% with the addition of panitumumab. In patients with mutated KRAS, there was no difference in efficacy. In terms of safety, there were differences in the incidence of skin toxicity and hypomagnesaemia between the panitumumab and the control arms of the study (37% *vs* 2% and

3% *vs* < 1%, respectively), and a 4% increase in grade 3 to 4 events such as diarrhoea, due to the overlapping toxicities between the EGFR inhibitor and irinotecan regimen[3].

The phase Ⅲ PICCOLO trial investigated the potential benefits of adding panitumumab to irinotecan in patients with aCRC, progressing after fluoropyrimidine treatment with or without oxaliplatin. Four hundred and sixty patients, including KRAS wild-type and those who had not been treated previously with EGFR targeting agents, were randomized to irinotecan alone or irinotecan-panitumumab (IrPan group). There was no difference in OS between the groups (HR = 1.01; 95%CI: 0.83-1.23; P = 0.91), but the patients in the IrPan group had longer PFS rates (HR = 0.78; 95%CI: 0.64-0.95; P = 0.015) and a greater response rate (34% *vs* 12%; P < 0.0001) than patients in the irinotecan group[19].

In KRAS wild-type patients who had not previously been exposed to a first-line treatment with a combination containing an anti-EGFR, or who had been treated with chemotherapy plus bevacizumab, an option is to add an anti-EGFR to chemotherapy (with panitumumab, in second-line, which is only approved in combination with FOLFIRI).

Anti-VEGF in the second-line setting

The efficacy of bevacizumab, in combination with the FOLFOX4 regimen in previously treated aCRC patients, was proven in a randomized phase Ⅲ trial in which 829 patients pretreated with fluoropyrimidine and irinotecan were randomly assigned to receive oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) with or without bevacizumab, or bevacizumab alone.

The median OS (primary endpoint) for the group treated with FOLFOX4 and bevacizumab was 12.9 mo, compared with 10.8 mo for the group treated with FOLFOX4 alone (HR for death = 0.75; P < 0.0011), and 10.2 mo for those treated with bevacizumab alone. Furthermore, the combination of bevacizumab and FOLFOX4 resulted in a statistically significant improvement in PFS, when compared with those treated with chemotherapy alone (7.3 *vs* 4.7 mo; HR for progression = 0.61, P < 0.0001). FOLFOX4 plus bevacizumab was associated with a higher incidence of hypertension, bleeding, vomiting and neuropathy when compared with the doublet alone[8].

There are no randomized trials comparing irinotecan-based chemotherapy (FOLFIRI), with or without bevacizumab, as a second-line therapy in patients pretreated with first-line FOLFOX. A pooled analysis of published trials (11 publications, 435 patients) showed a pooled response rate of 26%, with median PFS and OS of 8.3 and 17.2 mo, respectively. This analysis shows that FOLFIRI-bevacizumab is a reasonable and effective option for aCRC pretreated with oxaliplatin, and not exposed to bevacizumab in first-line therapy[20].

Patients treated in the first-line with a chemotherapy regimen including an anti-EGFR, or patients with a KRAS mutation could, therefore, benefit from bevacizumab in second-line therapy.

For patients treated with a first-line bevacizumab-containing chemotherapy regimen, the continuation of bevacizumab beyond the first progression with a second-line fluoropyrimidine-based chemotherapy can be considered, particularly for those with a KRAS mutation, who would not benefit from the use of an EGFR-targeted therapy.

The Bevacizumab Regimens' Investigation of Treatment Effects (BRiTE) study was a large, observational, bevacizumab treatment study in which baseline characteristics, bevacizumab-related adverse events, and effectiveness data were collected from 1953 metastatic colorectal cancer (mCRC) patients who were receiving first-line treatment including bevacizumab. One-thousand four-hundred and forty-five of the 1953 patients with mCRC who were enrolled in the BRiTE study, and who experienced disease progression, were classified into three groups: no post-progression treatment (n = 253), post-progression treatment without bevacizumab (n = 531), and post-progression treatment with bevacizumab (n = 642). The median OS was 25.1 mo (95%CI: 23.4-27.5 mo), and median PFS was 10.0 mo in the overall BRiTE population. In multivariate analyses, the use of bevacizumab beyond progression, compared with a second-line treatment not containing bevacizumab, was strongly and independently associated with improved survival (HR = 0.48; P < .001) with a median OS of 31.8 mo. Hypertension that required medication was the only bevacizumab-related side effect that occurred more frequently in the group of patients treated with a bevacizumab-containing regimen beyond progression (24.6% *vs* 19.2%)[21].

Other data supporting the use of bevacizumab beyond progression came from the ARIES study, a community-based observational cohort study that evaluated the effectiveness and safety of first-line treatment patterns. An analysis of 1074 patients, who progressed after first-line bevacizumab-containing treatments, evaluated 390 patients who were treated in second-line with an irinotecan-based regimen ± bevacizumab, and 114 patients treated with an oxaliplatin-based therapy, (always as second-line) ± bevacizumab. In patients receiving second-line irinotecan or oxaliplatin-based chemotherapy, the post-progression survival in the bevacizumab-treated patients was longer when compared to those not on bevacizumab (HR = 0.52, 0.40-0.67, for irinotecan-based + bevacizumab; HR = 0.5, 0.23-1.14, for oxaliplatin-based + bevacizumab)[22].

In a more recent, open-label phase 3 study, 409 patients affected by mCRC, progressing up to 3 mo after discontinuing first-line bevacizumab plus chemotherapy, were randomly assigned in a 1:1 ratio to second-line chemotherapy with or without bevacizumab at 2.5 mg/kg per week. The median OS was 11.2 mo (95%CI: 10.4-12.2) for bevacizumab plus chemotherapy and 9.8 mo (8.9-10.7) for chemotherapy alone (HR = 0.81; 95%CI: 0.69-0.94; unstratified log-rank test, P = 0.0062),

showing that continuing VEGF inhibition with bevacizumab, plus standard second-line chemotherapy beyond disease progression, has clinical benefits in patients with mCRC[23].

Additional data supporting the use of bevacizumab beyond progression comes from the phase Ⅲ BEBYP trial by the Gruppo Oncologico Nord Ovest. In this study (results presented at ASCO 2013), 184 patients with aCRC treated in the first-line with bevacizumab plus fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI were randomized to receive FOLFOX6 or FOLFIRI in the second-line, with or without bevacizumab. After a median follow-up of 22 mo, an improvement in the PFS for the study arm with bevacizumab was confirmed (5.2 mo *vs* 6.7 mo; HR = 0.66; 95%CI: 0.49-0.90; unstratified $P = 0.0072$). The benefit in terms of PFS was consistent in all subgroups considered[24].

An alternative option in the second-line for patients with mCRC, which is resistant to or has progressed following an oxaliplatin-containing regimen, is the combination of aflibercept and FOLFIRI. Aflibercept is a fusion protein with key domains for human VEGF receptors 1 and 2 with human IgG Fc[25] that blocks all human VEGF-A isoforms, VEGF-B and placental growth factor[26].

The approval of aflibercept in combination with FOLFIRI in this setting of patients was based on the placebo-controlled VELOUR trial, in which 1226 patients with mCRC that had progressed during or within six mo of receiving oxaliplatin-containing chemotherapy, with or without bevacizumab, were randomized to FOLFIRI with aflibercept (4 mg/kg Ⅳ) or placebo every two weeks until progression. Median OS was significantly longer in patients treated with aflibercept (13.5 *vs* 12.1 mo) as was the median PFS (6.9 *vs* 4.7 mo)[7]. The improvement in OS was consistent, regardless of prior treatments with bevacizumab.

CONCLUSION

In recent years, the introduction of new active drugs, and the development of new strategies in the management of advanced colorectal cancer, have enriched the second-line setting with several options that allow a more personalized treatment, with the perspective of treating the patient with all active agents available (obviously considering expected toxicities).

Fit patients seem more likely to be treated with all active drugs, starting in the first-line with a combination therapy (irinotecan or oxaliplatin-based). Regarding the chemotherapy backbone, a switch to an irinotecan-based treatment (in cases where the patient has been treated with an oxaliplatin-based regimen in the first-line) is, in general, the best choice; however, following FOLFOX failure, irinotecan and FOLFIRI are appropriate options. In the context of anti-angiogenic drugs, bevacizumab is approved in combination with a fluoropyrimidine-based regimen, and is an option to consider in the second-line, even beyond the first progression following a previous bevacizumab-containing therapy; additionally, aflibercept is a new option in combination with FOLFIRI. In KRAS patients, panitumumab can be used in the second-line in combination with FOLFIRI with patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan). Cetuximab is indicated in combination with irinotecan-based chemotherapy, and in combination with irinotecan alone in those patients who have failed a previous treatment with an irinotecan-based regimen. No clear superiority between targeted agents in the second-line has been shown, as reported by the SPIRITT trial. This was a randomized phase Ⅱ study, evaluating panitumumab + FOLFIRI *vs* bevacizumab + FOLFIRI in patients with wild-type KRAS mCRC previously treated with a bevacizumab + oxaliplatin-based chemotherapy in the first-line. In this trial there was no difference in the OS and PFS between the 2 treatment arms[27].

With so many options to consider, one cannot definitively state which is the best second-line treatment choice. The ongoing COMETS study, a GISCAD trial, is attempting to clarify this point by comparing two different sequences of therapy, irinotecan/cetuximab followed by FOLFOX-4 *vs* FOLFOX-4 followed by irinotecan/cetuximab, in mCRC patients treated with FOLFIRI/bevacizumab as the first-line chemotherapy.

The best strategy is presently unknown. A tailored sequence of treatments should be planned and proposed to patients by the beginning of the first-line therapy. With this in mind, the COMETS trial was designed. From the discussions between patients and physicians, bearing in mind the objective of the treatment and patient performance status and preference, the choice of second-line therapy will be decided, as in other phases of the disease history.

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