Review

Maintenance Therapy in Colorectal Cancer: Moving the Artillery Down While Keeping an Eye on the Enemy

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Abstract

The survival improvement in metastatic colorectal cancer, achieved with more intensive chemotherapy regimens, has recently led clinicians to question the optimal duration of therapies and to consider the role of maintenance. Indeed, patients whose disease is controlled after induction chemotherapy may benefit from continuing a less intensive regimen in order to reinforce the results achieved with up-front treatment. In addition, the more favorable toxicity profile of maintenance approaches would ensure a better quality of life. After discussing the rationale and the difference of pursuing a maintenance strategy with chemotherapeutic and/or biologic agents, we present significant available data from the literature and comment on the current implications and future directions of maintenance therapy. The current roles of depotentiated treatment schedules, antiangiogenic compounds, epidermal growth factor receptor inhibitors, and novel targeted therapies are also reviewed. Finally, we address elements that may foster clinical and social debate on this topic, suggesting potential aspects that need to be further investigated.

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Introduction

Although curative rates remain low for patients with metastatic colorectal cancer (CRC), the median overall survival (OS) is now more than 30 months in molecularly selected cases.1,2 The introduction of irinotecan and oxaliplatin, the widespread up-front use of biologic agents, and the milestone progress achieved in molecular biology3 have all contributed to improve outcome results to unprecedented levels.4 In addition, with the introduction of more intensive up-front combinations including drugs with potential cumulative toxicities, the common practice of continuing first-line chemotherapy until disease progression or unacceptable toxicity has changed, raising the question of optimal treatment duration.5 Whether first-line treatment should be continued until disease progression or discontinued as soon as a response has been achieved is debated.6 Indeed, there is limited evidence supporting the prolongation of first-line treatment beyond 4 to 6 months,7 and modern trials suggest avoiding treatment continuance beyond 6 months.8 At the time of tumor reassessment, oncologists may face 3 possible scenarios. If initially unresectable disease eventually becomes resectable, patients may be referred for salvage curative surgery.9 Conversely, if the disease has progressed, the patient may undergo second-line systemic treatment.3 Finally, if the disease is stable or it has even shrunk yet remains unresectable, patients might be considered for maintenance therapy.5 Although treatment discontinuation has been addressed with perplexity, especially for those patients with optimal performance status and who experience limited cumulative adverse effects, continuing chemotherapy may cause excessive toxicity with reduced quality of life and may potentially induce drug resistance. In this landscape, maintenance therapy represents a compelling alternative, which might keep the disease under control without the intensity of a full-regimen treatment. In the quest for the optimal maintenance strategy, 2 different strategies may be considered. The first is based on the concept of intermittency; it can involve either preplanned drug holidays or clinically driven treatment breaks. The second strategy is more focused on the intensity of the treatment. In such cases,
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Maintenance includes either a depotentiated combination of the upfront therapy or a completely different compound to which the patient has not previously been exposed (Figure 1). Finally, whenever medical oncologists decide whether patients need to continue to receive treatment or can take a drug holiday, the patients’ desires should always be taken into account. We completed a narrative literature review on maintenance therapy for patients with metastatic CRC, searching for eligible studies using the Medline database.

Clinical Concept of Maintenance

In patients with disease not amenable to salvage treatments, maintenance therapy aims at extending the favorable results obtained with the first-line induction therapy. Drug holidays or less intensive treatments ensure less toxicity as well as fewer hospital visits with increased quality of life. Treatment breaks may also result in cost savings. Maintenance encompasses continuous maintenance, where a less-toxic part of the former regimen is used until disease progression, and switch maintenance, where patients are exposed to novel non-cross-resistant cytotoxic drugs or targeted agents that were not included in the previous induction treatment (Figure 1). Optimal candidates must have experienced disease control with the induction therapy—namely, a response, or at least disease stabilization. Consequently, the current availability of more active first-line treatments increases the number of potential candidates for maintenance therapy. Initial induction treatment followed by de-escalation of cytotoxic drugs and planned maintenance treatment is gaining credibility, and recent data in the literature suggest that maintenance treatment may play a key role in different cancer types such as lung, breast, and ovarian carcinomas.

Cellular and Molecular Biology Underpinning Appropriateness of Maintenance Therapy

Most patients with metastatic disease experience progression, either while receiving chemotherapy as a result of intrinsic drug resistance or after an initial response as a result of an acquired drug resistance. Understanding the cellular and molecular biology underpinning drug resistance permits improving outcomes of CRC patients and planning more effective treatment strategies. The administration of 5-fluorouracil (5-FU) with either irinotecan or oxaliplatin to fluoropyrimidine-resistant CRC cells modulates thymidylate synthase activity, implicated with the response to 5-FU treatment; their reintroduction after disease progression is considered a rational strategy to overcome 5-FU resistance for patients initially treated with 5-FU—based combinations who had then received maintenance chemotherapy with 5-FU alone. Accordingly, even if at the cost of higher rates of neutropenia or peripheral neuropathy, a significant response rate was observed with second-line combination regimens in clinical trials recruiting patients with 5-FU—refractory disease.

Epidermal growth factor receptor (EGFR) signaling inhibition may resensitize tumor cells to irinotecan/SN38, leading to clinically significant effects in irinotecan-refractory CRC patients. Similarly, cetuximab may increase the tumor response to oxaliplatin-based chemotherapy in oxaliplatin-resistant disease, reducing the activity of ERCC1, a DNA excision repair protein that mediates the removal of platinum adducts. The use of up-front combinations including EGFR inhibitors should therefore be limited to patients with no mutations in RAS and possibly BRAF genes.
Notably, EGFR inhibitors may not be optimal for maintenance therapy because of the early emergence of acquired resistance to EGFR inhibitors, which typically occurs within few months after starting the therapy.44-46 Recent data indicate that different genetic alterations in the EGFR-RAF-MEK pathway or the amplification of receptor tyrosine kinases, including HER2 or MET,57 may cause resistance. Specific target mutations in the extracellular domain, such as the novel missense EGFR mutation S492R, may also cause secondary resistance.48 Preclinical studies suggest that the escape from anti-EGFR blockade tends to converge on the (re)activation of MEK-ERK49 or AKT,50 and the early identification of those underlying mechanisms via liquid biopsies may lead to a rational development of additional treatments.51

Instead, a more promising maintenance strategy involves the use of antiangiogenic drugs.52 CRC cells have a delayed onset pattern of growth inhibition, and vascular endothelial growth factor (VEGF) blockade is not immediately reflected by a change in tumor growth.53 Bevacizumab may induce reversible shrinkage in hypervascularized tissue,54 but a pro-angiogenic rebound after drug discontinuation has also been documented.55 Similarly, rapid disease progression has been shown during treatment interruptions in patients with renal cell tumors treated with pazopanib or sunitinib.56 Even if the mechanism underpinning the angiogenic rebound is still unclear, it appears to be related to the VEGF produced by the host stroma.57 Thus, prolonged exposure to antiangiogenic drugs may block the paracrine production of pro-angiogenic factors and may ultimately control tumor growth.58 Although antiangiogenic therapy reduces vascular permeability and delays disease progression, it may ultimately promote an aggressive treatment-resistant phenotype. In human CRC tumor cells, high hypoxia-induced factor VEGF signaling intensity due to autocrine VEGF signaling correlates to bevacizumab resistance.59 Recently, nintedanib has demonstrated antitumor activity in CRC models with intrinsic bevacizumab-resistant cells,60 showing that antiangiogenic-based maintenance strategies may be effective in preventing growth rebound in bevacizumab-resistant CRC cells. Whether the choice of chemotherapy modulates and induces acquired resistance to VEGF inhibitors remains to be investigated.61 Also, preclinical data about hypoxia and oxaliplatin activity are interesting. The formation of platinum adducts was reduced in hypoxic cells exposed to oxaliplatin, and oxaliplatin was consequently less effective in hypoxic compared to aerobic CRC cells. However, when hypoxia-induced factor 1 is inhibited, oxaliplatin adducts formation was restored.56,62

**Maintenance in CRC: Clinical Evidence**

**How Long Should CRC Patients Be Treated With First-Line Therapy?**

Discontinuing chemotherapy after a preplanned number of cycles is now considered with less skepticism. Although this strategy may be disadvantageous for a few patients, continuing treatment indefinitely is not actually supported by any strong evidence. A pivotal phase 3 trial enrolled 354 patients with disease that responded to up-front 5-FU or raltitrexed, and randomized them to either continuing the same treatment or temporarily discontinuing chemotherapy that was resumed later at disease progression. Despite only 37% of the patients recommencing treatment, no survival difference was observed among treatment arms (median OS, 11.3 vs. 10.9 months; hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.69-1.09; P = .23; similar survival rates at 2 years).63 The COIN study, a randomized controlled phase 3 trial, randomized 1630 previously untreated patients with advanced CRC to receive continuous versus intermittent oxaliplatin-based therapy.64 The primary end point was the noninferiority between the 2 treatment arms, with a predefined noninferiority boundary of 1.162 for intention-to-treat and per-protocol analyses. In the intention-to-treat analysis, the median OS was longer for patients who received continuous treatment (15.8 vs. 14.4 months; HR, 1.08; 95% CI, 1.00-1.16), as it was in the per-protocol analysis (19.6 vs. 18 months; HR, 1.08; 95% CI, 0.98-1.19). The 2-year survival rate was 28.3% versus 26.1% in the intention-to-treat analysis, and 34.8% versus 31.1% in the per-protocol analysis. Although the trial formally failed to demonstrate its primary noninferiority end point, a detrimental effect greater than 2.3 months in the intermittent arm was excluded. Moreover, intermittent chemotherapy was associated with improved quality of life and with a reduced number of visits to the hospital.

A recent systematic review and meta-analysis of randomized controlled trials comparing continuous versus intermittent treatments has shown similar results with the 2 strategies.65 Even when the analysis is restricted to those trials comparing continuous chemotherapy with no maintenance therapy at all, no survival difference was observed (HR, 1.03; 95% CI, 0.94-1.14; P = .5). The meta-analysis included a phase 3 Italian trial,66 in which 337 patients were randomized to receive FOLFIRI every 2 weeks continuously or FOLFIRI on a 2 months on/2 months off schedule, until disease progression. No difference in median progression-free survival (PFS; 6 months in both arms) or in median OS (18 vs. 17 months; HR, 0.88) was reported, suggesting that both strategies can be used. Not surprisingly, the intermittent schedule may be less expensive and better tolerated. Unfortunately, the above-mentioned meta-analysis included only 2 trials that tested modern treatment regimens. In this view, intermittent strategies should be discussed with the patient, but the noninferiority of a treatment break cannot be ruled out in patients exposed to first-line chemotherapy in combination with biologic agents. From another point of view, tumor shrinkage and disease control may be necessary to symptom control and consequently quality-of-life improvement. Because quality-of-life data from maintenance studies are limited, the potential advantages deriving from intermittent strategy in terms of safety have to be evaluated, considering the impact of tumor burden on global patient health.

**Which Is the Best “Maintenance” Approach?**

Because fluoropyrimidines are well tolerated, have limited cumulative toxicities, and may be given orally,67 these agents are optimal candidates for maintenance. In the OPTIMOX1 trial, 620 patients with unresectable CRC were randomly assigned to receive FOLFOX4 until progression or a stop-and-go strategy encompassing 6 cycles of FOLFOX7 followed by infusional 5-FU and leucovorin (LV5FU2) maintenance for up to 12 cycles, which ultimately might be followed by the reintroduction of the initial regimen in patients with controlled disease.68 Results showed no significant difference in median PFS (9.0 vs. 8.7 months), median OS (19.3 vs. 21.2 months), or overall response (58.5% vs. 59.2%) between treatment arms, with a more favorable toxicity profile for the intermittent arm. OPTIMOX2
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compared the fluoropyrimidine-based maintenance strategy with an intermittent approach and evaluated whether maintenance could be replaced by a “chemotherapy-free interval” after FOLFOX induction. More than 600 CRC patients were randomized to 6 cycles of modified FOLFOX7 (mFOLFOX7), followed by either maintenance with LV5FU2 or a treatment break. In both cases, the reintroduction of mFOLFOX7 was planned at disease progression. The primary end point was the duration of disease control, defined as the time sum of the initial PFS plus the PFS after reintroduction. Although the study was prematurely closed because of the approval of bevacizumab in first-line treatment, patients who had actually received maintenance therapy had a significantly longer median duration of disease control (13.1 vs. 9.3 months; HR, 0.71; P = .046), longer median PFS (8.6 vs. 6.6 months), and longer median OS (23.8 vs. 19.5 months) compared to those who dis continued treatment.

The greatest experience of maintenance therapy achieved so far is with antiangiogenic agents because strong biologic and clinical rationales suggest the use of bevacizumab until (and perhaps beyond) disease progression.

The first indirect demonstration of the benefit of the use of bevacizumab until disease progression came from the NO16966 study, in which PFS was longer when the antiangiogenic therapy was maintained until disease progression. Although the general PFS differed by only 1.4 months between treatment arms (9.4 vs. 8.0 months; HR, 0.83), the difference in median PFS was remarkably greater when considering on-treatment patients (10.4 vs. 7.9 months; HR, 0.63). In the CONNeCT trial, patients were randomized to receive mFOLFOX7 plus bevacizumab indefinitely until disease progression or 8 cycles of mFOLFOX7 plus bevacizumab followed by 8 cycles of maintenance LV5FU2 plus bevacizumab with the reintroduction of the initial regimen at progression. Patients enrolled onto the intermittent arm had a longer time to treatment failure (5.6 vs. 4.2 months; HR, 0.58) and a longer time to progression (12 vs. 7.5 months; HR, 0.53), suggesting, despite the very attenuated trial sample, that an intermittent schedule may produce a significant benefit versus continuous dosing.

In the Spanish Macro-TTD trial, 408 advanced CRC patients were randomized to receive either XELOX and bevacizumab until progression or unacceptable toxicity, or 6 cycles of the same regimen followed by bevacizumab alone. The primary study end point was PFS, with a noninferiority limit of 7.6 months (HR, 1.32), assuming a median PFS of 10 months in the control arm. Median PFS was similar among treatment arms (10.3 vs. 9.7 months; HR, 1.10), but because the HR interval crossed the preplanned noninferiority boundary (95% CI, 0.89-1.35), the study should be formally considered as negative, and noninferiority cannot be ruled out. However, we were confident in excluding a median detriment in PFS of more than 20 days, and we concluded that single-agent bevacizumab may be considered a maintenance therapy option.

More recently, CAIRO3 and AIO KRK 0207, 2 North European randomized studies, have set the standard for maintenance therapy with bevacizumab. CAIRO3 was designed to investigate the efficacy of maintenance treatment with metronomic capecitabine and bevacizumab. Patients with advanced unresectable CRC with responsive or stable disease after 6 cycles of oxaliplatin, capcitabine, and bevacizumab were randomly assigned to capecitabine (625 mg/m² 2 times a day continuously) plus bevacizumab (5.5 mg/kg every 3 weeks) or observation alone. The primary end point of the study was PFS2, defined as the time from randomization to progression upon reintroduction of the initial treatment. PFS2 corresponded to PFS1 in patients for whom bevacizumab and CAPOX were not reintroduced after progression. Patients were balanced between treatment arms, with 279 allocated to the maintenance arm and 279 to the observation arm. Notably, the induction treatment was reintroduced in only 60% of the patients assigned to the observation arm and in 47% assigned to the maintenance arm. PFS2 was longer in the maintenance arm (11.7 vs. 8.5 months; stratified HR, 0.67; 95% CI, 0.56-0.91; P < .0001; adjusted HR, 0.64; 95% CI, 0.53-0.76). An even greater difference was observed in PFS1 (8.5 vs. 4.1 months; stratified HR, 0.43; 95% CI, 0.36-0.52; P < .0001). Despite the advantage in PFS1 and PFS2, the OS was longer but the difference observed was not statistically significant (21.6 months in the maintenance arm vs. 18.1 months in the observation arm; stratified HR, 0.89; 95% CI, 0.73-1.07; P = .22). Interestingly, patients with a response after induction treatment had a greater benefit from maintenance treatment compared to those with stable disease. A higher incidence of severe neutropenia (10% vs. 5%) and hand-foot syndrome (22% vs. 0) was observed in patients who received maintenance therapy. Nevertheless, no difference in quality of life was reported between treatment arms. Despite a slightly higher incidence of hypertension in the maintenance arm (24% vs. 18%), the incidence of venous thromboembolic events (3% vs. 2%) and gastrointestinal perforations (1% vs. 0) was similar.

In the AIO KRK 0207 trial, a total of 476 patients with metastatic or unresectable CRC who had at least stable disease after 6 months of bevacizumab plus an oxaliplatin-based chemotherapy, were randomly allocated to bevacizumab with fluoropyrimidine (arm 1, considered as the standard arm), bevacizumab alone (arm 2), or observation (arm 3). The aim of the trial was to test the noninferiority of observation or bevacizumab alone compared to the combination arm, and a noninferiority HR limit was set at 1.43. Time to failure of the strategy was the primary end point of the study, defined as the time elapsed from randomization to either the second progression after maintenance and reintroduction or, in case of no reintroduction, the use of a second-line drug or no further treatment. Secondary end points included PFS, OS, and toxicity analysis during maintenance treatment with time-specific quality-of-life assessments. Maintenance treatment was continued until progression, unacceptable toxicity, or patient refusal, or until it was no longer considered to be in the interest of the patient’s care. The noninferiority of bevacizumab alone compared to bevacizumab and 5-FU was demonstrated (median tumor-free survival, 6.5 vs. 6.8 months; HR, 0.98; 95% CI, 0.76-1.26; P = .85); conversely, the noninferiority was not reached for the observation alone arm because the HR confidence interval crossed the prespecified boundary of 1.43 (median tumor-free survival for observation, 6.1 months; HR, 1.22; 95% CI, 0.96-1.57; P = .11). Because the rate of full chemotherapy reintroduction was much lower than expected, the primary trial end point could be biased by the significant rate of dropouts usually reported in previous CRC trials investigating stop-and-go or maintenance strategies. Nevertheless, OS was similar among treatment arms (23.8 vs. 26.2 vs. 23.1 months). Consistent with the results of the CAIRO3 trial, the maintenance treatment was well tolerated and caused no excess toxicities.
Potential Role of EGFR Inhibitors in Maintenance Strategy

Cetuximab and panitumumab target the extracellular domain of EGFR, thus inhibiting cell proliferation and promoting tumor apoptosis in KRAS wild-type patients. Because of the potential development of acquired resistance after prolonged drug exposure and their specific safety profile, limited data on maintenance with EGFR inhibitors are available. The COIN-B study evaluated the safety and tolerability of cetuximab in combination with intermittent chemotherapy. The randomized phase 2 trial enrolled metastatic CRC patients to intermittent oxaliplatin-based chemotherapy plus intermittent or continuous cetuximab. The primary study outcome was failure-free survival at 10 months that ultimately resulted similar among treatment arms (50% in the intermittent arm, 52% in the continuous arm).

Different mechanisms involving alternative pathways, such as the VEGF pathway, might be responsible for the emergence of acquired resistance to EGFR inhibitors. Although only preclinical evidence is currently available, there is a remarkably growing biologic rationale to consider the VEGF pathway, might be responsible for the emergence of acquired resistance after prolonged drug exposure and their specific safety profile. Limited data on maintenance with EGFR inhibitors are available. The COIN-B study evaluated the safety and tolerability of cetuximab in combination with intermittent chemotherapy. The randomized phase 2 trial enrolled metastatic CRC patients to intermittent oxaliplatin-based chemotherapy plus intermittent or continuous cetuximab. The primary study outcome was failure-free survival at 10 months that ultimately resulted similar among treatment arms (50% in the intermittent arm, 52% in the continuous arm).

Novel Molecules in Maintenance Strategy

The synergistic combination of erlotinib and bevacizumab was tested in preclinical models and in pivotal clinical trials. The aim of the GERCOR DREAM trial was to study the possible survival impact of the combination maintenance with erlotinib (150 mg/day orally, continuously) plus bevacizumab (7.5 mg/kg every 3 weeks) after induction treatment with chemotherapy and bevacizumab. In this phase 3 study, patients with advanced CRC who received up-front chemotherapy plus bevacizumab for 6 months were randomly assigned to bevacizumab alone (n = 224) or bevacizumab plus erlotinib (n = 222). The trial met its primary end point: median PFS was 9.3 months for bevacizumab alone compared to 10.2 months for bevacizumab in combination with erlotinib (HR, 0.76; 95% CI, 0.61-0.94; P = .009), and such results were confirmed regardless of the KRAS mutational status. However, no difference in OS was observed (median OS, 27.9 vs. 28.5 months; HR, 0.89; P = .312), with higher frequency of severe diarrhea (9% vs. 1%) and skin toxicity (20% vs. 0) reported in the experimental arm. Although the lack of OS benefit may be partially explained with the number of subsequent lines of therapy diluting the effect of front-line treatment, the median advantage in PFS (less than 1 month) was too limited to outweigh the increased toxicity and economic costs.

MGN1703 is a novel, dumbbell-shaped molecule that can potently stimulate the innate immune system through its action on the Toll-like receptor agonist. A small randomized, placebo-controlled phase 2 trial tested MGN1703 as maintenance treatment in 59 advanced CRC patients with disease control after standard first-line therapy (88%) or without bevacizumab (22%). The primary end point of the study was PFS, defined as the time elapsed from randomization to progression while receiving maintenance therapy. Although the median PFS while receiving maintenance therapy was similar (2.8 vs. 2.6 months), a clear advantage in HR was observed in favor of the experimental drug (HR, 0.55; 95% CI, 0.3-1.0; P = .004) as a result of the presence of a small subgroup of patients with a long PFS at 9 months (20% vs. 0; P = .006). MGN1703 was more active in patients with CRC that had previously achieved significant tumor shrinkage (median, 24.5 vs. 15.1 months; HR 0.40). Even if the very small trial sample size does not permit us to draw definitive conclusions, MGN1703 maintenance treatment might induce durable disease control in selected patients. The phase 3 IMPALA study will further test this strategy and is currently recruiting patients.

Efatutazone is a third-generation thiazolidinedione that acts as a highly selective peroxisome proliferator-activated receptor gamma agonist. Preclinical studies have shown that efatutazone inhibits human CRX tumor xenograft growth, and early clinical studies have demonstrated an acceptable tolerability profile. Recently, a placebo-controlled, multicenter phase 2 study randomized 84 CRC patients who had experienced disease control after standard first-line treatment with efatutazone (0.5 mg administered orally twice daily) or placebo. The trial met its primary end point: the PFS rate at 18 weeks was 39.9% (95% CI, 23.5-55.7) in the efatutazone group and 25.0% (95% CI, 13.0-39.0) in the placebo group (HR, 0.66; P < .0001). Median PFS was 3.0 months in the efatutazone group and 2.7 months in the placebo group (P = .03); median OS was 22.9 months in the efatutazone group and 12.8 months in the placebo group (P = .12), although the study was not powered to

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1 EudraCT number 2015-000333-71 has been issued for the Sponsor’s Protocol Code Number Valantino, according to the investigator’s personal information.
demonstrate any difference in survival. Notably, the experimental treatment caused more hematologic toxicity and fluid retention.

Metronomic chemotherapy may also contribute to tumor control,95,96 and this approach has recently gained renewed interest because of its possible synergistic association with molecular targeted agents. Metronomic chemotherapy may mediate its action through angiogenesis inhibition, direct cytotoxic activity, and immunomodulation. Several preclinical studies on human CRC xenografts have demonstrated that low-dose cyclophosphamide, tegafur–uracil, capcitabine, and topotecan may all have antitumor activity. Small clinical trials have investigated metronomic schedules including capcitabine or cyclophosphamide and suggested their synergistic effect with bevacizumab. The phase 2 MOMA trial is testing the role of metronomic chemotherapy in combination with bevacizumab after FOLFOXIRI and bevacizumab as induction treatment.

Clinical trials investigating the role of maintenance therapy in CRC according to different strategies are summarized in Table 1.
Can We Afford the Cost of Maintenance?

In a time of growing costs for cancer care, the value of maintenance therapy and its sustainability should be carefully considered. Value is a composite ratio between benefits and costs, which includes price, toxicity, and time spent for each in-hospital treatment, although there is no consensus on its definition in cancer care. Cost-effective analyses showed conflicting results on the up-front use of bevacizumab for CRC patients treated within clinical trials and in a real-world setting, and set for the use of the angiogenic inhibitor an incremental cost of around US$75,000 per life-year gained in older patients. Recent clinical trials have demonstrated that the continuation of bevacizumab compared to observation alone may prolong the median PFS of approximately 1.5 months. This result, however, is achieved with significant additional health care expenditures. As expected, a cost analysis showed a significantly greater value for patients who received bevacizumab as maintenance therapy compared to those who did not, with an average value of US$37,596 and US$8180, respectively; this suggests that the usefulness of maintenance bevacizumab must be balanced by a careful cost analysis. Interestingly, different studies showed that a cautious dose rounding of biologic drugs may be cost effective without any loss in efficacy, and these observations may be transferred to maintenance treatment as well. An acceptable cost for quality-adjusted life-year has not been definitively established in Western countries, but it hardly deviates from a range between US$50,000 and US$150,000 per quality-adjusted life-year. Therefore, we probably need to update our assessment tools, mainly by increasing the comparative effectiveness research across different treatment strategies. In the meantime, we can reasonably expect that regulatory agencies may raise the bar of efficacy for drug approval.

Conclusion

The treatment of patients with disease not amenable to cure should aim to achieve disease control, delay progression, and improve survival. These results should be pursued while avoiding cumulative toxicity, improving patients’ quality of life, and maintaining sensitiveness to any given agent. On these premises, preclinical evidence and clinical trials have shown the importance of maintenance therapy in responsive or stable metastatic CRC patients. This approach may encompass either a less intensive treatment with more favorable toxicity profile or treatment breaks. In both cases, quality of life would be improved, and drug holidays may even result in health care savings. However, some key clinical issues remain unsolved, such as the optimal duration of first-line treatment and the value of maintenance therapy itself. On the basis of the available results, it appears reasonable to start patients on an induction treatment with chemotherapy and targeted agents for periods no longer than 6 months and then offer maintenance therapy to selected candidates. In this landscape, bevacizumab, alone on in combination with fluoropyrimidines, is the most extensively investigated drug. Despite a growing amount of evidence from randomized trials supporting its efficacy in the maintenance setting, the widespread use of bevacizumab is still debated. A number of reasons account for this skepticism, including the lack of predictive factors for angiogenic inhibitors, the difficulties when evaluating drug efficacy with classic Response Evaluation Criteria in Solid Tumors, and the undefined frequency of the radiologic assessments during maintenance. Importantly, because the median gain in PFS achieved with maintenance is of a few months, we need to consider the costs that such a strategy would impose in a time of restricted financial resources. Although bevacizumab appears safe and effective in this setting, more cost-effective data are needed to further endorse its general use. The biologic rationale and the clinical evidence for using EGFR inhibitors as maintenance is less convincing. However, a more accurate molecular selection of patients with disease that has a greater chance of responding might support future studies. Novel compounds are currently tested as maintenance agents, thus enriching the future available options. For the time being, maintenance therapy should be considered a valuable option for selected patients rather than a standard of care. It remains unclear, however, which patients may benefit the most from continuing first-line treatment without drug holidays.

Disclosure

The authors have stated that they have no conflicts of interest.

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