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REVIEW ARTICLE

From Complexity to Simplicity: Best Level of Evidence for Metastatic Colorectal Cancer

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ABSTRACT

Simplicity is enormously complex in the treatment of metastatic colorectal cancer. In terms of survival, life expectancy of patients with metastatic colorectal cancer improved substantially from 3 to 6 months in the 1980s when only 5-fluorouracil was available, to more than 20 months today with the availability of various new chemotherapeutic and targeted agents. The use of chemotherapeutic agents — including fluoropyrimidines, irinotecan, and oxaliplatin — has been refined through decades of clinical experience. Maximal exposure, irrespective of sequence, is simply the principle of treating patients through progression with chemotherapy. Targeted therapy has emerged in the past decade, and adds complexity to the treatment principle: survival benefit has been shown with both anti–vascular endothelial growth factor and anti–epidermal growth factor receptor antibodies in individual lines of treatment, but controversy exists as to the best sequence of application. Adding to this complexity, evidence continues to evolve for the predictive value of various key biomarkers as well as the development of new agents, including aflibercept and regorafenib. In this review, the best level of evidence and a simple, yet practical, strategy will be discussed for maximising the overall survival of patients.

Key Words: *Chemotherapy, adjuvant; Colorectal neoplasms; Receptor, epidermal growth factor; Vascular epidermal growth factor*

中文摘要

從複雜到簡單：轉移性結直腸癌的最佳證據

林嘉安

要簡單地治療轉移性結直腸癌其實是相當複雜的。上世紀80年代治療轉移性結直腸癌的藥物只有5-氟尿嘧啶，當時患者的壽命一般約為3至6個月，直至現在因各種新的化療和靶向藥物的出現，令患者生存期大幅提高至20個月以上。經過數十年的臨床經驗，化療藥物（包括氟尿嘧啶、伊立替康和奧沙利鉑）的使用已得到完善。化療的主要原則簡單來說是在癌症的不同階段中，不論藥物使用的先後次序，盡量讓患者接受到各種化療藥物。靶向治療早在過去的十年經已出現，它增加了治療原則的複雜性：在各種治療線上出現的抗血管內皮生長因子和抗表皮生長因子受體抗體經已證明它們有助延長生存期，可是對治療的最佳次序仍存在爭議。同時，各種關鍵生物標誌物的預測值，以及新的藥物如aflibercept和regorafenib，亦增加了治療的複雜性。本文會討論最佳的研究證據，以及既簡單又實用的策略來把患者的總生存期延至最長。

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INTRODUCTION

According to data from the Hong Kong Cancer Registry, colorectal cancer (CRC) is the second most common cancer in terms of both incidence and mortality.[1] It is estimated that 20 to 25% of patients with CRC present at a late stage and, for those who present with early stage disease, around 30 to 35% will have a recurrence. With the exception of patients whose metastatic disease is amenable to curative resection, most patients with metastatic CRC (mCRC) will require palliative treatment. As a result of recent advances in systemic therapy, the median survival of patients with mCRC has markedly improved from 3 to 6 months with best supportive care to 14 to 20 months with combination chemotherapy[2-5] and, more recently, exceeded 20 months with the addition of targeted therapy.[6-9] However, the availability of more agents not only leads to prolongation of survival, but also results in growing complexity of the treatment algorithm. Oxaliplatin, irinotecan, bevacizumab, and cetuximab have been available for over 10 years with robust data showing patients' survival prolonged to different extents by different drugs given at different lines of treatment.[2-8] Nevertheless, the lack of head-to-head comparisons for the various regimens in prospective randomised trials has led to ambiguity in the choice and sequencing of the different regimens. The latest data for panitumumab,[9] aflibercept,[10] and regorafenib[11] have added to the complexity of the treatment algorithm. It is with this complexity in mind that the available evidence is reviewed and a simplified treatment algorithm proposed. Although the goals of palliative treatment include arresting tumour progression and maintaining quality of life, the proposed treatment algorithm is based on maximising overall survival as a robust endpoint of outcomes with regard to the choice of targeted therapies. The Table[6,8-21] summarises the current status of the available targeted agents.

SURVIVAL IS THE GOAL: SIMPLIFYING THE TREATMENT ALGORITHM

Principle of Use of Chemotherapy

Chemotherapy plays a central role in the efficacy of systemic therapy against mCRC. Using 5-fluorouracil (5FU) as the treatment backbone, the addition of oxaliplatin and / or irinotecan improves the response rate and survival of patients at the cost of manageable toxicities. Oxaliplatin is known for neurotoxicity and hypersensitivity, while irinotecan causes more haematological and gastrointestinal side-effects.[5] Unlike irinotecan, oxaliplatin has minimal activity as a single agent.[22,23]

As a relevant discussion to the topic of simplicity in a treatment algorithm, maximum exposure to all agents regardless of sequence is the main principle of use of chemotherapy. The importance of maximising exposure to all available chemotherapeutic agents was highlighted by a regression analysis performed by Grothey et al.[24] Their study showed that the overall survival correlated significantly with the percentage of patients who received all three chemotherapeutic agents (5FU, oxaliplatin, and irinotecan) in seven phase III clinical trials involving 1991 patients. The result was validated subsequently by four additional large phase III trials in mCRC and a mathematical equation was derived: overall survival in months = 13.2 + (percentage of patients receiving all three agents x 0.1).[25] Although their regression model did not aim to predict the overall survival of patients treated with the chemotherapy triplet, data from the Gruppo Oncologico Nord Ovest study group showed a similar finding.[26]

It is well established that the actual sequence of use of each chemotherapeutic agent does not influence the overall survival. In a phase III randomised controlled

Table. Current status of different targeted agents in Hong Kong.

	Bevacizumab	Cetuximab	Panitumumab	Aflibercept	Regorafenib
Approval status in Hong Kong	Approved	Approved	Named patient	Named patient	Named patient
Improves OS in unselected patients*	Yes[6]	Yes[8]	No	Yes[10]	Yes[11]
Improves OS in KRAS WT patients	Yes[12,13]	Yes[14,20]	Yes[9]	NR	Yes[11]
Improves OS in first-line therapy	Yes[6]	Yes[14]	Yes	NA	NA
Improves OS in second-line therapy	Yes[15,16]	No[17]	No[18]	Yes[10]	NA
Improves OS in third-line therapy and beyond	No[19]	Yes[20]	No[21]	NA	Yes[11]

Abbreviations: OS = overall survival; WT = wild-type; NR = not reported; NA = not applicable.
* Unselected patients refer to those patients who were unselected for KRAS status.

trial by Tournigand et al,[27] the overall survival of patients who received FOLFOX (5FU, leucovorin, oxaliplatin) followed by FOLFIRI (5FU, folinic acid, irinotecan) or vice versa was not significantly different. Similar conclusions can be drawn from the FOCUS[28] and the CAIRO[29] studies, which prospectively randomised patients to combination or sequential chemotherapy treatment. In both studies, the outcomes of patients who received initial single-agent treatments were not inferior to those started with combination therapy.

Nevertheless, the above principle has not yet been confirmed for targeted agents. From the results of the PACCE (Panitumumab Advanced Colorectal Cancer Evaluation[30]) and CAIRO2[31] studies, maximising exposure by concurrent use of vascular endothelial growth factor antibodies (anti-VEGF) and epidermal growth factor receptor antibodies (anti-EGFR) may cause a detrimental impact on survival. In addition, data from small retrospective studies suggest that the benefit of using targeted agents may be sequence-specific, although firm conclusions cannot be drawn until data from randomised controlled studies are available.[32,33] Thus, the following discussion is based on the assumption that the benefit in each line of treatment is additive and there is no carry-over effect to subsequent lines of treatment.

Evidence for First-line Treatment

Bevacizumab was the first targeted agent to improve overall survival in the first-line treatment of patients with mCRC.[6] In the landmark AVF2107 study, 813 patients were randomised to irinotecan, bolus fluorouracil, and leucovorin (IFL) with or without bevacizumab.[6] Statistically and clinically significant improvements in response rate (44.8% vs. 34.8%; $p = 0.004$), progression-free survival (10.6 vs. 6.2 months; hazard ratio [HR] = 0.54; $p < 0.001$), and overall survival (20.3 vs. 15.6 months; HR, 0.66; $p < 0.001$) were demonstrated. As the only study to show an overall survival benefit with bevacizumab in the first-line setting, the study was criticised for using a less effective regimen as the control arm since IFL is inferior to regimens containing infusional 5FU in terms of efficacy and toxicity. In fact, bevacizumab failed to improve overall survival and response rate of patients in the NO16966 study, in which patients received either FOLFOX or XELOX (capecitabine, oxaliplatin) in the control group.[7] Nevertheless, the study met its endpoint of improving progression-free survival (9.4 vs. 8.0 months; HR = 0.83; $p = 0.0023$) and provided insights into the importance of continuing bevacizumab treatment until disease progression.

So far, there is no validated predictive biomarker for bevacizumab. A retrospective analysis of 230 patients from the AVF2107 study with available tissue samples for molecular testing has shown that KRAS status is not predictive of clinical efficacy of bevacizumab.[12] This is further supported by a recent pooled analysis of seven randomised controlled trials which found that the efficacy of bevacizumab is independent of age, performance status, extent of disease, chemotherapy backbone, and KRAS status.[13]

Unlike treatment with anti-VEGF antibodies, patient selection is the key to success in the treatment with anti-EGFR antibodies, although results from various clinical trials have shown conflicting results. The CRYSTAL study was the first phase III randomised controlled trial to show a survival benefit for cetuximab in first-line treatment of mCRC.[8] Compared with FOLFIRI alone, the addition of cetuximab improved response rate (57.3% vs. 39.7%; odds ratio [OR] = 2.069; $p < 0.001$), progression-free survival (9.9 vs. 8.4 months; HR = 0.696; $p = 0.0012$), and overall survival (23.5 vs. 20.0 months; HR = 0.796; $p = 0.0093$) in the KRAS wild-type subgroup. A similar magnitude of benefit in response rate (OR = 2.16; $p < 0.0001$), progression-free survival (HR = 0.66; $p < 0.001$), and overall survival (HR, 0.81; $p = 0.0062$) was demonstrated in the pooled analysis of the CRYSTAL and OPUS studies.[14] The PRIME study randomised 1183 patients to FOLFOX with or without panitumumab and a prospective analysis of KRAS status was incorporated.[9] Recent updated results confirm a statistically and clinically significant improvement in overall survival (23.8 vs. 19.4 months; HR = 0.83; $p = 0.027$). In contrast, the COIN and NORDIC VII studies showed conflicting results. The COIN was the largest study by number of patients, and prospective analyses of KRAS, NRAS, and *BRAF* status were included.[34] The chemotherapy backbone was oxaliplatin with infusional 5FU or capecitabine. Although a marginal improvement in overall response rate (64% vs. 57%; OR = 1.35; $p = 0.49$) was observed, cetuximab conferred no benefit in either progression-free or overall survival. In the NORDIC VII study, cetuximab did not improve the efficacy of oxaliplatin and bolus 5FU with regard to all study endpoints.[35] The negative results of this study might have been anticipated as the study was designed with a greater

than 80% power to detect an increase in progression-free survival from 7 to 10 months, a magnitude that has never been seen with anti-EGFR antibodies. In short, the prevailing body of evidence supports the use of anti-EGFR antibodies in first-line treatment of KRAS wild-type mCRC and a consistent improvement in response rate is the strength of anti-EGFR antibodies. However, consideration should be given to the choice and schedule of the chemotherapy regimen.

To date, there has not been much evidence on which to base the choice of first-line targeted agent. However, two of the three ongoing head-to-head prospective studies comparing bevacizumab with cetuximab / panitumumab were presented at the American Society of Clinical Oncology 2013 annual meeting and the European Society of Medical Oncology 15th World Congress on Gastrointestinal Cancer meeting. The PEAK study is a multicentre phase II randomised study comparing bevacizumab with panitumumab using the modified FOLFOX-6 regimen as the chemotherapy backbone.[36] The two treatments showed no difference in progression-free survival, the primary endpoint of study, among KRAS wild-type patients, but there was a difference in toxicity profile as anticipated; there was a higher incidence of hypertension with bevacizumab and more diarrhoea and skin rash with panitumumab. The FIRE-3 study is another head-to-head comparison that has triggered much debate.[37] This is a multicentre phase III randomised study comparing bevacizumab with cetuximab, with overall response rate as the primary objective. Compared with bevacizumab, cetuximab added to FOLFIRI did not improve the response rate or the progression-free survival in KRAS wild-type patients, but the overall survival was significantly improved (28.7 vs. 25.0 months; HR = 0.77; p = 0.017). The improvement in overall survival should be interpreted with caution in the context of an unmet primary endpoint. Moreover, the two survival curves on the Kaplan-Meier plot overlap initially and separate only after 10 to 12 months, which is far beyond the median duration of treatment and just beyond the median progression-free survival of the whole population. A significant effect of post-progression treatment will be a logical assumption in this situation. Knowing that exposure to post-progression treatment is balanced numerically, one should also look at the relative efficacy of the second-line treatment. Second-line cetuximab plus oxaliplatin-based regimens in the bevacizumab arm may not be equivalent to bevacizumab plus oxaliplatin-based regimens in the cetuximab arm. In view of the unresolved questions, the results of the Cancer and Leukemia Group B 80405 study (ClinicalTrials.gov: NCT00265850), the largest of three studies, are eagerly awaited.

In summary, the jury is still out as to the best first-line targeted agent until the three studies are fully published. There are also emerging data on the significance of RAS mutation status that may affect treatment decisions.[38] Currently, the benefit of anti-EGFR antibodies is restricted to KRAS wild-type patients, while patients with significant cardiovascular comorbidities should not receive bevacizumab. Both anti-VEGF and anti-EGFR antibodies are evidence-based choices with different toxicity profiles.

Evidence for Second-line Treatment

Most patients who progress with first-line treatment are still sufficiently fit to receive second-line therapy. It is estimated that up to 70 to 80% of patients will receive any form of second-line treatment and that around 40% will receive targeted therapy in this setting.[36,37] Anti-angiogenic therapies, including bevacizumab and aflibercept, have more robust evidence for survival benefit than anti-EGFR antibodies in the second-line setting.

In the Eastern Cooperative Oncology Group (ECOG) E3200 study, the addition of bevacizumab to FOLFOX-4 significantly improved the response rate (22.7% vs. 8.6%; p < 0.0001), progression-free survival (7.3 vs. 4.7 months; HR = 0.61; p < 0.0001), and overall survival (12.9 vs. 10.8 months; HR = 0.75; p = 0.0011) in patients previously treated with a fluoropyrimidine and irinotecan.[15] The relative lack of single-agent activity of bevacizumab was demonstrated in the third arm of the study since bevacizumab alone showed a response rate of only 3.3% and progression-free survival of only 2.7 months. The clinical benefit of anti-angiogenic therapy in the second-line setting has recently been echoed by the results of the VELOUR[10] and the ML 18147[16] studies. Aflibercept is a novel fusion protein that binds VEGF-A, VEGF-B, and placental growth factor. In the VELOUR study, 1226 patients who had been treated with oxaliplatin with or without prior bevacizumab were randomised to receive FOLFIRI and aflibercept or placebo.[10] The magnitudes of benefit were similar to those of the ECOG E3200 study for response rate (19.8% vs. 11.1%; p = 0.0001), progression-free survival (6.9 vs. 4.7 months; HR = 0.76; p < 0.0001), and overall survival (13.5 vs. 12.1 months; HR = 0.82, p = 0.0032).

In a pre-specified subgroup analysis, the effects on progression-free survival and overall survival showed a consistent and favourable trend regardless of any pretreatment with bevacizumab.

Since angiogenesis is crucial to every step in tumour progression, continual inhibition of angiogenesis appears to be logical. The clinical benefit of continual VEGF inhibition was first demonstrated in the BRiTE[39] and ARIES[40] observational studies, in that patients who continued bevacizumab beyond first progression appeared to have prolonged survival. The ML 18147 study was designed against this background, and randomised 820 patients who had progressed after standard first-line bevacizumab-containing treatment.[16] Patients who had more aggressive disease (i.e. progression-free survival of <3 months with first-line treatment) and who sustained no benefit from first-line bevacizumab (i.e. treatment with bevacizumab of <3 months) were excluded. The results were consistent with the BRiTE[39] and ARIES[40] studies that progression-free survival (5.7 vs. 4.1 months; HR = 0.68; $p < 0.0001$) and overall survival (11.2 vs. 9.8 months; HR = 0.81; $p = 0.0062$), but not the response rate (5% vs. 4%; $p = 0.31$), were improved by bevacizumab. Subsequent analysis also confirmed that the efficacy of bevacizumab beyond progression is independent of KRAS mutation status.[41]

Although the efficacies of bevacizumab and aflibercept are comparable in the second-line setting, bevacizumab appears to have a better toxicity profile. In the VELOUR study, adverse events that led to treatment discontinuation occurred in 26.6% and 12.1% of patients in the aflibercept and placebo groups, respectively.[10] Compared with placebo, aflibercept increased both chemotherapy-related and anti-angiogenic therapy–related toxicities, including diarrhoea, neutropenia, and hypertension.

Unlike anti-angiogenic therapies, the use of anti-EGFR antibodies has not significantly improved overall survival in phase III randomised controlled studies. Nevertheless, both cetuximab and panitumumab have been shown to improve progression-free survival significantly. The EPIC study investigated the effect of second-line irinotecan with or without cetuximab in patients who had progressed with oxaliplatin and fluoropyrimidines.[17] Longer progression-free survival (4.0 vs. 2.6 months; HR = 0.692; $p < 0.0001$) and higher response rate (16.4% vs. 4.2%; $p < 0.0001$) were observed with the addition of cetuximab. However, in the 181 study, panitumumab significantly prolonged progression-free survival (5.9 vs. 3.9 months; HR = 0.73; $p = 0.004$) and improved response rate (35% vs. 10%; $p < 0.001$) in the KRAS wild-type cohort.[18] It should be reminded that there are no prospective data on the use of anti-EGFR antibodies beyond first progression as both studies excluded patients with prior anti-EGFR antibody treatment.

In summary, the use of anti-angiogenic therapy in the second-line setting is supported by robust data from phase III randomised controlled trials. Whether or not patients were treated with bevacizumab in the first-line setting, bevacizumab and aflibercept demonstrated significant activity in prolonging survival. Bevacizumab is preferred in view of its better toxicity profile, while aflibercept will be reserved for the more aggressive tumours that do not respond well to first-line treatment. The use of bevacizumab allows enhanced treatment exposure. In KRAS wild-type tumours that require more rapid disease control, cetuximab and panitumumab are still feasible options in view of their favourable response rates.

Evidence for Third-line Treatment and Beyond

There is an unmet need for effective treatment in the third-line setting and beyond as patients have usually exhausted all available agents in the first two lines of treatment. Bevacizumab appears to have limited activity in this setting. The National Cancer Institute Treatment Referral Center TRC 0301 study was the first and largest prospective single-arm phase II study to examine the efficacy of bevacizumab and 5FU after prior treatment of oxaliplatin- and irinotecan-based chemotherapy.[19] A very low response rate of 4% was reported, while progression-free and overall survival was 3.5 and 9 months, respectively. However, anti-EGFR antibodies have demonstrated consistent clinical benefit in this setting. The National Cancer Institute of Canada Clinical Trials Group CO.17 study was a phase III randomised study that recruited patients who had failed or were contraindicated for fluoropyrimidine, oxaliplatin, and irinotecan.[20] Compared with best supportive care, cetuximab significantly prolonged median progression-free survival (3.7 vs. 1.9 months; HR = 0.40; $p < 0.001$) and overall survival (9.5 vs. 4.8 months; HR = 0.55; $p < 0.001$) in the KRAS wild-type subgroup. The results reflect the actual benefit of cetuximab as very few patients receive further systemic therapy after

progression on cetuximab. Panitumumab has efficacy in line with that of cetuximab. In the 408 study, patients who had failed oxaliplatin- and irinotecan-based therapy were randomised to panitumumab or best supportive care.[21] In the pre-planned subgroup analysis of KRAS wild-type patients, panitumumab significantly improved progression-free survival (12.3 vs. 7.3 weeks; HR = 0.45; $p < 0.0001$). Due to crossover of patients post-progression, a significant improvement in overall survival was not observed. The response rates of single-agent cetuximab and panitumumab were 12.8% and 17%, respectively, in the KRAS-wild-type subgroup. The above data should be interpreted with caution as they are specific to a group of targeted therapy-naïve patients.

For targeted therapy of pre-treated patients, regorafenib is the therapeutic option with the greatest evidence base. Regorafenib is an oral multi-kinase inhibitor that is also known as a 'dirty drug' since it interacts with numerous targets in oncogenic, stromal, and angiogenic pathways. The CORRECT study enrolled patients who had failed all approved standard therapies, including anti-EGFR and anti-VEGF therapies.[11] In this study, 753 patients were randomised 2:1 to best supportive care with regorafenib or placebo. The primary endpoint of the study was met, with significant improvement in overall survival (6.4 vs. 5.0 months; HR = 0.77; $p = 0.0052$). Although the absolute increase in survival was just over 1 month, the 23% improvement reflected by the HR should not be taken lightly in this group of treatment-refractory patients. The toxicity profile is a concern as grade 3/4 adverse events, including hand-foot skin reaction, fatigue, diarrhoea, hypertension, and rash, occurred in more than 5% of patients.

In summary, anti-EGFR antibodies are the preferred choice for patients who have had no prior exposure, while regorafenib is an option for desperate patients who are treatment-refractory. In these scenarios, the anticipated benefit is small and has to be balanced against the toxicities. Patients should be counselled and realistic goals set.

CONCLUSION

The principle behind this simplified algorithm is to maximise treatment exposure and be proactive in the whole process of treatment planning. The treatment algorithm proposed here is based on the best available evidence for prolonging survival in patients who are fit

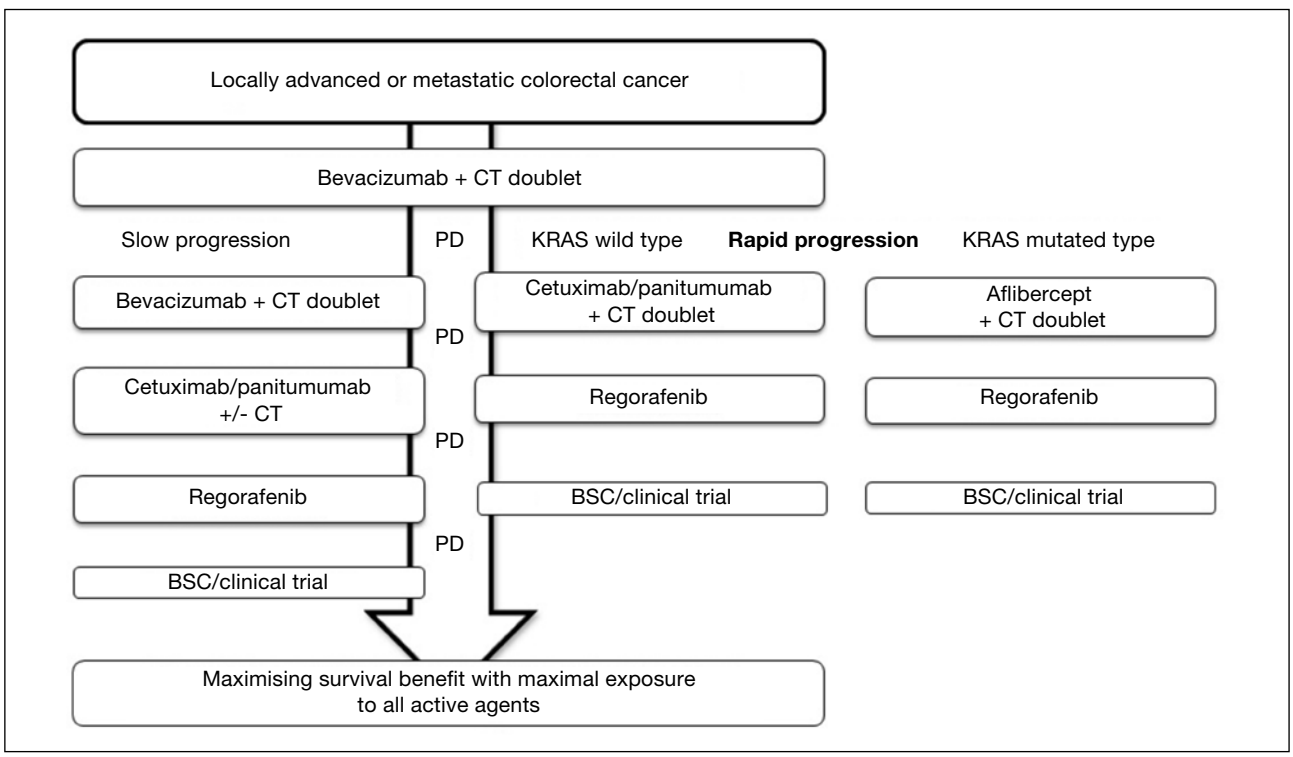

Figure. Simplified treatment algorithm.

Abbreviations: CT = chemotherapy; PD = progressive disease; BSC = best supportive care.

for aggressive systemic therapy (Figure). Therapy for patients who have primary treatment goals other than this is outside the context of the current discussion. Looking into the future of personalised medicine, more predictive and prognostic biomarkers should be validated, best chemotherapy-targeted agent couples defined, and the optimal sequence of targeted agents determined. New drugs targeting MET, insulin-like growth factor, and hepatocyte growth factor signalling pathways are in the pipeline and tumour immunotherapy is another new area of research. In personalised medicine, this is not the beginning of the end, this is just the end of the beginning!

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