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Metastatic colon cancer: is rechallenging still an option beyond second line? A quick review.

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Metastatic colon cancer: is rechallenging still an option beyond second line? A quick review.

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Abstract

Metastatic colorectal cancer continues to be very frequent and although the improvements in its systemic treatment throughout the past decade have been noticeable, much needs still to be done. Patientsâ€™ survival has been prolonged with good quality of life, being still suitable for further treatment, thus further options are expected and demanded by them. The fact is that in heavily treated patients, therapy options are lacking. Beyond second-line, there is no optimal treatment and many have tried a reintroduction of previous chemotherapeutic regimens or biological treatments (such as epidermal growth factor receptor (EGFR) inhibitors used in pretreated patients) although limited evidence exists. Trifluridine/tipiracil has shown a benefit in overall survival when administered to patients who failed on previous chemotherapy and biological treatments. Regorafenib was approved by the US Federal Drug Administration for these patients and no difference has been found between these last two options. Concepts have changed then and a multiline strategy has been defended. What we need is a better knowledge about tumour biology and predictive factors of response so a tailored treatment could be possible one day. At this time we should aim for further strategic clinical trials which seem to be urgently needed.

Introduction

Colorectal cancer (CRC) continues to be the third most frequent malignancy around the world with one fourth of cases being already metastatic (mCRC) at diagnosis. Although significant advances have been achieved in its treatment, with numerous new drugs available, most patients will develop progressive disease and eventually die (1,2). The overall survival (OS) for this group continues to be low (3) and much research is still needed to change dramatically this situation.

Currently, the standard treatment in first and second line settings is chemotherapy alone or in combination with a vascular endothelial growth factor (VEGF) targeted agent or for those patients with KRAS wild type, an epidermal growth factor receptor (EGFR) targeted treatment. These combinations will achieve a median OS of 23-24 months (m) (4).

However, these patients will eventually develop progressive disease and many of them will reach this situation in a good clinical condition, being still suitable for further therapy.

In the past, oncologists reused previous chemotherapy lines although many patients did show only marginal benefits or did not show any benefit at all. Â

Currently, further agents are available for standard use. Regorafenib, a multitargeted tyrosine kinase inhibitor (TKI) (5,6), and trifluridine/tipiracil (another cytotoxic combination, also known as TAS 102) (7,8). The main issue here is the lack of availability of these agents in different countries, which leave the oncologists with empty hands.Â

Few further new agents are already a reality but either not approved for standard routine use or still under research.

This situation opens the question about what to do with these patients who demand further lines of treatment beyond second line if no other option is available, not even a clinical trial to be recruited.

Is re-challenging previous treatments still an option for each patient, or only for those who did not show any evidence of progression before?

Are there any ways of recovering sensitiveness?

It is clear that a long discussion about current aims of treatment and what potential impact is it going to have on patientâ€™s quality of life is mandatory. Even more, patients who developed significant toxicities before, should they be spared further toxicity taking into account that the expected benefits are going to be smaller?

Clearly there is much to do to uncover the best strategy for these patients and hopefully further approvals are coming soon. But in the meantime, several variables should be taken into account (such as patient-related issues, molecular profiling, disease volume, clinical trials) to develop a tailored approach.

This is a brief overview of the evidence available about rechallenging treatments already used.

Review

RECHALLENGING PREVIOUS TREATMENTS

Chemotherapy alone or in combination with monoclonal antibodies (MoAbs) is the standard of care in first and second line treatment for mCRC. Beyond that, 63.3% patients are still fit to receive a third line and 45.9% to receive a fourth line (9).

Four regimens have been recommended in the last National Comprehensive Cancer Network Guidelines (NCCN) for mCRC in third or later lines: anti-EGFR MoAbs with or without irinotecan, regorafenib; TAS 102; and programmed cell death protein-1 (PD-1) inhibitors (this in patients with DNA mismatch repair deficiency dMMR) (10).

However, these lines have limited efficacy and weak survival benefit; likewise, anti-EGFR MoAbs (with or without irinotecan) obtain an objective response rate (ORR) of 20-25.7%, with a time to progression ranging from 3.4 to 5.4 m and overall survival (OS) ranging from 8.0 to 10.4 m (11).

To give further light into this, regorafenib has shown to improve progression free survival (PFS) in 1.9 m compared to placebo with OS of 6.4 m according to results in the CORRECT trial (5).

And TAS 102, improves median OS from 5.3 m with placebo to 7.1 m, being the HR for death in the TAS-102 group of 0.68 (95% confidence interval [CI], 0.58 to 0.81; P< 0.001) (8).

Pembrolizumab â€“ a humanized MoAb that targets the PD-1 receptor- has shown ORR of 40% but only in dMMR CRC (12).

Therefore, treatment of CRC patients in third lines and beyond represent an important challenge to the physician: TAS 102 and regorafenib get scarce survival benefits, anti-EGFR Abs can only be used in 40% patients who do not harbour RAS mutations, and dMMR is only present in 3.5-5.0% of metastatic tumors.

In this setting physicians might consider the option of retreatment with drugs used in previous lines (oxaliplatin, bevacizumab associated to other treatments, capecitabine or 5FU, irinotecan, anti-eGFR, etc) even though they were stopped not because of toxicity but rather progression.

RECHALLENGING OXALIPLATIN

A retrospective study compared the outcomes of 95 patients with mCRC retreated with oxaliplatin-containing regimens with the results of 29 patients treated with EGFR antibodies and irinotecan in the control arm (13).

In the oxaliplatin arm, the ORR was 6.3% with no complete response (CR), but 6 patients (6.3%) had partial response (PR) and 39 (41.1%) achieved stable disease (SD). The disease control rate (DCR) was 47.4% with a median PFS of 3.77m and median OS of 12.17 m.

he authors did not find any significant difference between the two arms in PFS and OS and only patients who achieved disease control by re-exposure to oxaliplatin had a superior PFS and OS when compared with those who presented PD (6.13 vs 1.7 m, p< 0.001 and 15.73 vs 6.27 respectively).

Therefore, authors concluded that re-challenging with oxaliplatin-containing chemotherapy may lead to equivalent tumour control and survival benefit in mCRC to that of anti-EGFR combined with irinotecan.

Another study with 110 patients (38.2% had received oxaliplatin as adjuvant treatment and 61.8% as palliative chemotherapy) showed an ORR to oxaliplatin rechallenge of 30.9% and DCR 68.2%. Median PFS of 5.9 m (95% CI 4.4-7.4 m) and median OS 1.5 m (95% CI 14-23 m) (14).

Both previous studies have suggested that re-exposure to oxaliplatin-containing chemotherapy might be an alternative option in third and subsequent lines of therapy for patients who had already progressed on these regimens.

The OPTIMOX trial compared prospectively two regimens in 620 patients. One group was administered FOLFOX-4 until PD while the other group were treated with a â€œstop and goâ€• strategy. They received FOLFOX-7 for 6 cycles, followed by Leucovorin (LV), 5FU (5 fluorouracil) for 12 and FOLFOX-7 re-administration.

PFS and OS were similar in both groups although oxaliplatin was reintroduced only in 40% of patients in the group 2. Â (15)

De Gramont et al has published that the reintroduction of oxaliplatin was an independent factor with a significant impact on survival (Hazard ratio (HR) = 0.51, 95% CI 0.3 to 0.9, P = 0.009). (16)

Another study presented at the American society of clinical oncology (ASCO) 2009 meeting showed that PFS and OS were significantly better when the interval between oxaliplatins was more than 12 months. (17)

Re-challenging oxaliplatin in third-line seems to be an option for patients previously treated with it, mainly if oxaliplatin had been stopped due to toxicity and if the oxaliplatin-free interval was long.

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The OPTIMOX study does not support the reintroduction of oxaliplatin in patients who have progressed on it. However, it evidenced the relevance of this agent if it had been stopped Â because of temporary adverse events.

RECHALLENGING CAPECITABINE Â

With capecitabine in third-line the RR was 0%, and TTP 2.8 months. The most frequent adverse event were hand-foot syndrome and diarrhoea, with one dead due to febrile neutropenia.

Capecitabine as a monotherapy did not provide any clinical benefit. Â (18)

These data do not support the use of capecitabine or 5FU as single agents after the failure of doublet regimens.

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However, it has been used in combination with mitomycin C in third line. A small study with 21 patients, showed a RR 4.8%, with 19% stable disease. PFS 2.6 months and OS 6.8 months. (19)

Another study with 35 patients showed better results with a RR 15.2%, 48.5% of stable disease, PFS of 5.4 months and OS 9.3 months. (20)

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RECHALLENGING IRINOTECAN AND CETUXIMAB

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The multicenter, single-arm, phase 2 CRICKET trial assessed the role of a third-line retreatment with cetuximab plus irinotecan after an initial response followed by progression of the same regimen in the previous line. The objective of this trial was to determine if liquid biopsy could be used to select patients. Wild-type *RAS* and *BRAF* at baseline patients were recruited.

All patients received first-line with cetuximab and irinotecan and had shown at least a partial response (PR). After at least a PFS of 6 months and PD within 4 weeks of the last cetuximab dose, all patients received oxaliplatin and bevacizumab based second-line treatment. Following the second PD, all patients received cetuximab plus irinotecan until next PD. The primary endpoint was response rate.

Authors concluded that among patients with mCRC initially sensitive and then resistant to this regimen, this prospective study showed the first demonstration of the activity and it suggested as well that wild-type *RAS* detected in ctDNA may help identify those who would show a benefit from this approach. (21)

RECHALLENGING BEVACIZUMAB

Bevacizumab-based therapies have been examined in this setting as well.

Yang *et al* (22) conducted a retrospective study of 35 patients with mCRC who were treated with bevacizumab plus chemotherapy as a third or later-line.

Around 25% of patients had previous treatment with anti-VEGF. These authors reported a 20% of PR with Â 62.9% Â showing SD; the ORR was 20% and DCR 82.9%. Median PFS was 5.98 m (95% CI 4.76-7.2) and median OS 14.77 m (95% CI 11.45-18.1 m).

In the univariate analysis, PFS and OS were not linked to RAS mutation or prior anti-VEGF or anti-EGFR therapy. In fact, OS was 18.56 and 13.77 m for patients treated with or without previous anti-VEFR respectively, although there was no statistically significant difference (p=0.58).

According to these results, authors concluded that by adding bevacizumab to third or later-lines in mCRC, Â tumor control and OS may improve.

Although all these data come from retrospective studies and further prospective longitudinal studies are needed, patients in third lines and beyond might be retreated with oxaliplatin or bevacizumab-based regimens. It could be an alternative approach particularly in patients with RAS mutation tumours or proficient MMR where anti-EGFR and / or anti-PDL-1 are not a choice.

Conclusion(s)

The increase in long term OS in patients with mCRC have led to an elevation in the number of patients candidates to further lines of treatment. Even in heavily pre-treated patients, the option of retreatment is still available if ECOG performance status and functional tests are within an acceptable range.

Currently, it is not clear yet the best therapeutic sequence but it is generally accepted that if a patient has not received all relevant chemotherapy agents, those should be taken into consideration first.

With the approval of further drugs, it seems that chemotherapy re-challenges are old fashioned. However, the availability of the new agents is not widespread and in several areas, many patients are unable to receive them.

This is the most important context where a past therapy re-challenge might be considered.

The final choice of treatment will depend on prior used

drugs, on the patient performance status and the tumour biology. But a multiline strategy seems to be the most accepted approach nowadays. However, strategic trials are desperately awaited to establish the best final therapeutic regimen for each individual patient.

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