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Maximising clinical benefit with adequate patient management beyond the second line in mCRC

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ABSTRACT

New therapeutic options for refractory metastatic colorectal cancer (mCRC) include trifluridine/tipiracil (TAS-102) and regorafenib. However, the optimal chemotherapeutic regimen for use of each agent beyond the second line for patients with mCRC remains unclear and various factors may influence treatment decision. Available efficacy data suggest treatment with either trifluridine/tipiracil or regorafenib may be appropriate as both can extend patient survival. Thus, the safety profiles of each agent, along with patient performance status, are likely to determine treatment choice. The safety profiles of trifluridine/tipiracil and regorafenib are markedly different: higher levels of non-haematological adverse events such as fatigue, diarrhoea, hypertension and hand-foot skin reaction are reported with regorafenib, while haematological events such as neutropaenia are more common with trifluridine/tipiracil. In general, neutropaenia is a manageable treatment-related toxicity, while hand-foot skin reaction can be troublesome for patients, affecting their ability to carry out everyday activities and get on with their lives, while also affecting treatment adherence. Thus, the occurrence of any potential adverse effects and patient adherence should be closely monitored at each clinic visit. As quality of life is an important issue for patients with mCRC, it is important to balance extended survival and the likely quality of this extended life. Likewise, discussing possible side effects along with treatment expectations with patients can greatly facilitate adherence to therapy, and ultimately improve patients' quality of life and eventual clinical outcomes.

LAY SUMMARY

When therapies for colorectal cancer have similar beneficial effects on survival, different aspects of the drugs become important. These include the occurrence of side effects and their impact on quality of life, which can impact a patient's general well-being.

INTRODUCTION

In Europe, colorectal cancer (CRC) is the second most commonly diagnosed cancer and the second most common cause of oncological death.[1] Most patients with CRC will present with metastases at some point in the disease process, contributing to the high associated mortality rates: approximately 25% of patients present with this advanced disease at initial diagnosis, while half of those who do not will eventually develop unresectable metastases and become refractory to standard therapies soon after.[2] Although targeted therapy and a better molecular understanding of metastatic CRC (mCRC) have led to major improvements in patient survival for minority molecular subtypes of patients, most patients have limited therapeutic options when the disease becomes refractory.[3]

Many patients with mCRC refractory to standard chemotherapy continue to maintain good performance status (PS), remain candidates for further treatment and are typically motivated to follow this therapeutic approach[4]; however, available therapies offer only narrow risk to benefit ratios. New therapeutic options for mCRC have recently become available. Trifluridine/tipiracil (also known as TAS-102) is an oral formulation which consists of the nucleoside analogue trifluridine and tipiracil, which inhibits degradation of trifluridine,[5] while regorafenib is an orally available multikinase inhibitor.[3] However, the optimal chemotherapeutic regimen for use of each agent beyond the second line for patients with mCRC remains unclear and various factors may influence treatment decision. This paper will examine treatment goals in mCRC beyond second line, along with strategies for effective patient monitoring during treatment. It is based on a presentation given at the recent mCRC Masterclass 'Shaping tomorrow's mCRC treatment paradigms', which took place in Budapest on 13–14 April 2018.

TREATMENT GOALS ACCORDING TO LINE OF THERAPY

ESMO guidelines, definition of therapy lines and regimens

The optimal treatment strategy for patients with clearly unresectable mCRC continues to rapidly evolve.[3] Importantly, overall survival

(OS) depends on first-line therapy and on subsequent lines of therapy. Current European Society for Medical Oncology (ESMO) guidelines note that the management of patients with mCRC should be viewed as a 'continuum of care' in which determination of therapeutic goals is important; such goals include prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life (QoL). However appropriate selection of a first-line therapeutic approach is key, as this is the most active treatment line when it comes to tumour response, progression-free survival (PFS) and OS. In addition, first-line treatment will determine subsequent lines of therapy and thus the continuum of care. A defined treatment aim is important to allow the integration of a multimodal approach along with choice of first-line systemic treatment, while also supporting realistic patient expectations.[3] Finally, it is important to remember that therapeutic goals typically change according to the line of therapy being administered[3 6] (figure 1). For example, a reduction in tumour size ('shrinkage') no longer predominates in later lines of therapy, whereas maintained disease control and palliation of tumour-related symptoms using regimens with low toxicity become increasingly relevant.[6]

The effective implementation of later lines of therapy in mCRC requires most physician expertise given the reducing benefit/risk or 'narrowing therapeutic margin' with each subsequent line of systemic treatment.

According to ESMO consensus guidelines, the typical first-line chemotherapy backbone comprises a fluoropyrimidine (intravenous 5-fluorouracil [5-FU] or oral capecitabine) used in various combinations and schedules with irinotecan or oxaliplatin, and a monoclonal antibody.[3] Second-line therapy is that received from the time when the first-line chemotherapy backbone needs to be changed, typically after treatment failure, and should be offered to as many patients as possible.[3] Second-line therapy is generally proposed for patients with good PS and adequate organ function, and is dependent on the first-line therapy choice. Second-line therapy with oxaliplatin and irinotecan is known to be superior to best supportive care (BSC) and single agent 5-FU. If an anti-angiogenic agent has not been given first line, this therapeutic approach is often used second line; this is in contrast with anti- Epidermal Growth Factor Receptor (EGFR) agents which can also be given beyond second line if not used on earlier lines.

ESMO consensus guidelines recommend that either trifluridine/tipiracil or regorafenib is used in patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in *RAS* wild-type patients with EGFR antibodies.[3] Notably, a proposed algorithm for treatment decisions beyond the second line for mCRC suggests that either agent can be used prior to use of the other as later-line therapy.[7]

Characteristics of patients with mCRC treated with third-line treatments

When selecting a third-line treatment for a patient with mCRC, factors which require consideration include tumour-related and disease-related characteristics, such as clinical presentation and patterns of tumour biology, along with patient-related factors, such as patient

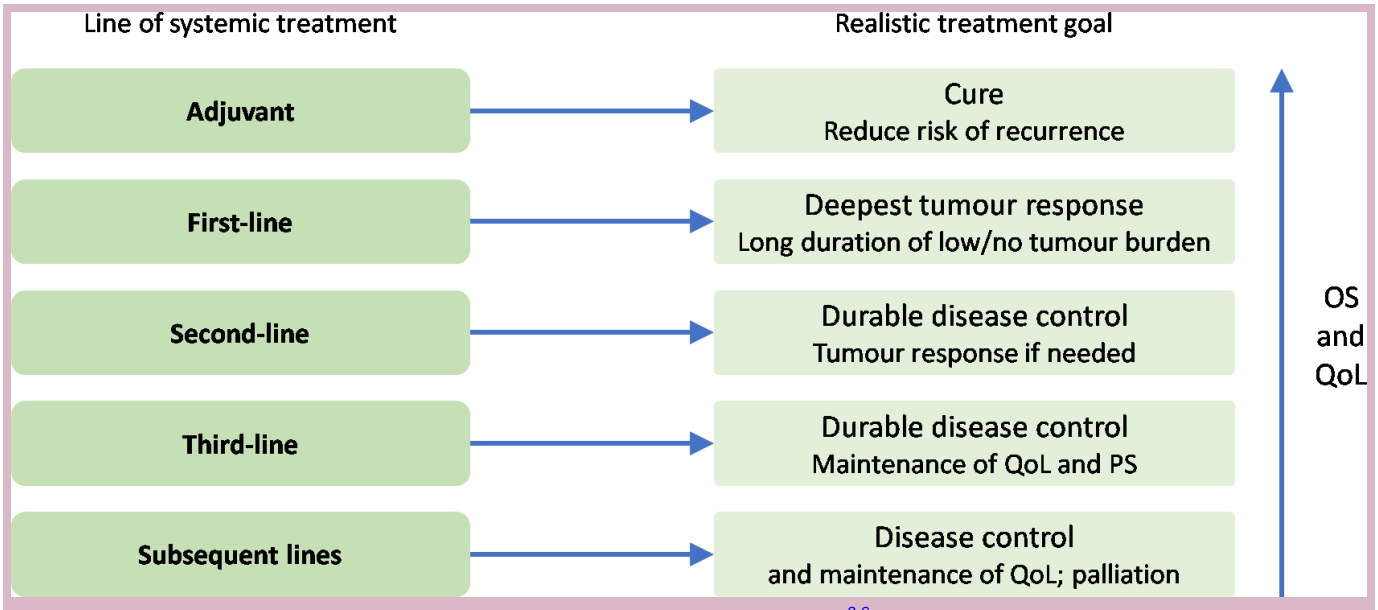

Figure 1 Treatment goals with line of therapy in metastatic colorectal cancer.[3 6] OS, overall survival; PS, performance status; QoL, quality of life.

Box 1 Key factors for consideration prior to planning a treatment strategy for metastatic colorectal cancer[3 8]

Overall condition and emotional status of patients.
- Fit versus unfit for a combination therapy (triplet vs doublet vs monotherapy).
- Eastern Cooperative Oncology Group performance status.
- Patient age.
- Established comorbidities.
- Patient attitude.
- Patient disease history (eg, previous oxaliplatin-based adjuvant treatment).

Tumour characteristics and clinical course.
- Indolent versus aggressive tumour.
- Disease presentation (synchronous vs metachronous).
- Tumour load.
- Mutational status (*RAS* and *BRAF*).

Treatment goal.
- Tumour shrinkage to achieve a radical surgery of metastases or palliation of disease-related symptoms.
- Disease control to delay progression and worsening of the patient's general condition.

expectations, expected toxicity and the presence of comorbid condition(s)[3 8] (box 1).

A retrospective comparison between trifluridine/tipiracil and regorafenib in 200 patients demonstrated that the majority of patients treated with third-line agents were fit patients.[9] In addition, an overview of patient profiles in the refractory setting demonstrated that patients receiving third-line or fourth-line treatment for mCRC had a European Cooperative Oncology Group (ECOG) PS of 0 or 1.[10] Data provided by phase III clinical studies correspond only to ECOG 0 or 1 patients, while real-world evidence coming from the REBECCA cohort, the CORRECT and RECOURSE trials, and Spanish real-world data includes also a subset of patients with ECOG >1, suggesting thereby that this subset of patients is not represented in clinical trials. Thus, conclusions from available clinical trial data are difficult to extrapolate to this patient population. It seems clear that therapeutic decisions for patients with ECOG PS of 2 need to be individualised for treatment with trifluridine/tipiracil or regorafenib, while there is not enough evidence for the use of these agents in patients with ECOG PS >2.[11–14] While treatment with trifluridine/tipiracil or regorafenib is appropriate in patients with mCRC and an ECOG PS of 0 or 1, physician expertise and the use of risk assessment tools such as the Colon Life nomogram[15] should be used to confirm if patients with an ECOG PS of 2 have a status more similar to ECOG PS 0–1 or 3–4, as these patients are often borderline cases and there is an ongoing need to discriminate between these two patient populations to ensure that the correct patient group is treated appropriately with trifluridine/tipiracil or regorafenib.

Evidence of treatment efficacy in mCRC: trifluridine/tipiracil or regorafenib

RECOURSE was a randomised, double-blind, phase III study of trifluridine/tipiracil plus BSC versus placebo plus BSC in patients with mCRC refractory to standard chemotherapies[12]; this study was conducted in Japan, the USA, Europe and Australia. In RECOURSE, the HR for death (trifluridine/tipiracil vs placebo) was 0.68 (95% CI 0.58 to 0.81; p<0.001); the median OS was 7.1 months (95% CI 6.5 to 7.8) and 5.3 months (95% CI 4.6 to 6.0), respectively. In RECOURSE, the majority (82%) of patients had received ≥3 prior lines of treatment. The superiority of trifluridine/tipiracil over placebo was particularly meaningful given that more than 90% of those patients participating in RECOURSE had disease previously refractory to fluoropyrimidines.

An updated survival analysis of RECOURSE has confirmed that the OS benefit of trifluridine/tipiracil relative to placebo was maintained over time compared with the original analysis.[16] The final OS analysis (including 89% of events, compared with 72% in the initial analysis) confirmed the survival benefit associated with trifluridine/tipiracil, with an HR of 0.69 (95% CI 0.59 to 0.81; p=0.0001). In addition, trifluridine/tipiracil was effective in all subgroups, regardless of age, geographical origin or *KRAS* status.

CORRECT was a randomised, placebo-controlled, phase III study in 16 countries in North America, Europe, Asia and Australia, to assess the efficacy and safety of regorafenib plus BSC versus placebo plus BSC.[11] In CORRECT, regorafenib significantly improved OS in pretreated patients with mCRC versus placebo, with 74% of regorafenib-treated patients having received ≥3 prior treatments. The median OS was 6.4 months in the regorafenib group vs 5.0 months in the placebo group (HR 0.77; 95% CI 0.64 to 0.94; one-sided p=0.0052). In addition, the 1-year survival rate was 24.3% in the regorafenib group and 24.0% in the placebo group at 1 year.

Based on available efficacy data, treatment with either trifluridine/tipiracil or regorafenib is an appropriate first choice beyond the second line in patients with mCRC. Thus, patients' PS and the safety profiles of each agent are likely to be important considerations when selecting treatment.

On the other hand, immunotherapy constitutes the preferred option for the infrequent microsatellite instable subtype that encompasses the 5% of the total mCRC population. The anti- programmed death receptor 1 (PD1) agents pembrolizumab and nivolumab reported groundbreaking response rates of nearly 30% and survival rates at 12 months of more than 70%, data that were later improved by the combination of nivolumab plus the anti- cytotoxy T-lymphocyte antigen 4 (CTLA4) ipilimumab which pushed the bar of efficacy up to 50% response rate and 85% of survivors at 12 months.[17–19]

The continuum of care beyond second line and the use of rechallenge

The increased number of potential treatment options for mCRC along with the use of some agents in more than one line or as adjuvant therapy can make the treatment landscape appear complex, with physicians finding it difficult to select appropriate treatments in the later lines of therapy.[20] A recent retrospective real-life study noted that the number of patients with mCRC who receive further treatment after first-line therapy progressively declines, although 40% and 20% of patients typically receive third-line or fourth-line treatment, respectively.[21] Importantly, the concept of the 'continuum of care' in the strategic choice of a regimen or sequence in the different lines of treatment for mCRC requires careful consideration.[3] Treatment choice will depend on multiple factors including molecular characterisation of the tumour, treatment goal, awareness that anti-EGFR antibodies also have a high activity in later lines of therapy, patient expectations and expected treatment toxicity.

Available evidence suggests that the efficacy of trifluridine/tipiracil and regorafenib on PFS and OS remains independent of prior use of either agent.[22] It remains important to highlight that clinically fit patients should be closely monitored while on treatment with either drug to allow an early switch to the other drug on progression. Trifluridine/tipiracil has proven to maintain a good PS (0 or 1) in the majority (84%) of patients at discontinuation, allowing for the administration of a further line of therapy.[23] In patients pretreated with regorafenib who manage to maintain a good PS (0 and 1), trifluridine/tipiracil has been shown to have a similar effect compared with patients not previously treated with regorafenib.[12]

Some physicians may rechallenge with irinotecan-based and oxaliplatin-based chemotherapy, fluoropyrimidines, bevacizumab, and either cetuximab or panitumumab for those with *RAS* wild-type tumours as later line treatment for mCRC after progression or recurrence before considering the use of trifluridine/tipiracil or regorafenib.[3 24] Unlike reintroduction of a treatment when there has been no progression on therapy, rechallenge involves administering a therapy to which the tumour has already developed resistance.[7] However, this approach is not an option if residual toxicity from previous chemotherapy is present, and it may lack efficacy in patients who have previously progressed on a similar regimen.[3 25 26] In addition, evidence for this strategy beyond second line remains limited in mCRC. A recent systematic review supports the introduction of approved agents such as trifluridine/tipiracil or regorafenib beyond the second line before any rechallenge in patients with mCRC who have failed second-line treatment.[20]

INFLUENCE OF SAFETY PROFILE IN PATIENTS BEYOND THE SECOND LINE

Safety profile of trifluridine/tipiracil and regorafenib

The safety profiles of trifluridine/tipiracil and regorafenib are markedly different, and it is important to highlight that both treatments should only be used in patients with good PS and adequate organ function.[3 7] A summary of the most common side effects for trifluridine/tipiracil and regorafenib is shown in table 1.

Adverse events associated with trifluridine/tipiracil are typically haematological and clinically asymptomatic in nature. In RECOURSE, grade ≥3 adverse events occurred in 69% and 52% of patients treated with trifluridine/tipiracil and placebo, respectively, with haematological toxicities the most common events; febrile neutropaenia occurred in 4% and 0% of patients, respectively.[12] An integrated summary of safety confirmed the safety profile observed in RECOURSE and highlighted consistency and predictability of adverse events based on comparison of available data safety sets with trifluridine/tipiracil.[16]

Adverse events associated with regorafenib are typically non-haematological.[11 27] In CORRECT and CONCUR, grade ≥3 adverse events occurred in 54% of patients (14% and 0% in the two placebo arms), with hand-foot skin reaction (HFSR), hypertension, fatigue, gastrointestinal symptoms, increased liver enzymes and hypophosphataemia reported as the most common events occurring at a higher frequency versus placebo. However,

Table 1 Most commonly reported (≥25%) side effects for trifluridine/tipiracil and regorafenib in phase III clinical studies[11 12]

Trifluridine/Tipiracil (n=533)[12]			Regorafenib (n=500)[11]		
	Overall	Grade ≥3		Overall	Grade ≥3
Leucopenia	77	21	Hand-foot skin reaction	47	17
Anaemia	77	18	Fatigue	47	9
Neutropaenia	67	38	Diarrhoea	34	7
Nausea	48	2	Anorexia	30	3
Thrombocytopaenia	42	5	Voice changes	29	<1
Decreased appetite	39	4	Hypertension	28	7
Fatigue	35	4	Oral mucositis	27	3
Diarrhoea	32	3	Rash/Desquamation	26	6

All data are shown as %.

recent data suggest that the dose–toxicity relationship with regorafenib can be managed by using a low starting dose, which can then be increased depending on toxicity. This flexibility of the starting dose can set the basis for a new pattern on the use of the drug.[28]

Differences in the safety profiles of trifluridine/tipiracil and regorafenib will influence choice of third-line or later-line treatment (ie, trifluridine/tipiracil or regorafenib). Thus, there is an ongoing need to predict and address potential adverse events in each patient when selecting treatment. When considering safety data from RECOURSE and CORRECT in similar patient populations, higher levels of non-haematological adverse events (fatigue, diarrhoea, hypertension and HFSR) were reported with regorafenib compared with trifluridine/tipiracil.[11 12] In contrast, neutropaenia was more commonly reported with trifluridine/tipiracil (any grade: 67%; grade ≥3: 38%) compared with regorafenib (any grade: 2.8%; grade ≥3: 0.6%).[11 12] Of note, treatment with trifluridine/tipiracil is associated with a low frequency of febrile neutropaenia.[12]

Trifluridine/tipiracil and regorafenib also differ in liver-related adverse events, which will need to be considered in patients with mCRC and limited hepatic function. Grade ≥3 hepatic-related/liver-related adverse events such as increases in alanine aminotransferase, aspartate aminotransferase and total bilirubin were greater with regorafenib (5.5%, 5.9% and 12.4%, respectively) compared with trifluridine/tipiracil (2%, 4% and 9%, respectively).[11 12] As regorafenib is metabolised via the liver, its use in patients with liver dysfunction remains a challenge, and it is important to ensure that a patient has proficient liver function prior to administration.[29] For observed elevations of alanine aminotransferase and/or aspartate aminotransferase >5 times the upper limit of normal (ULN) but ≤20 times the ULN, treatment with regorafenib should be interrupted and its use reassessed.[30] For trifluridine/tipiracil, no adjustment of the starting dose is recommended in patients with mild hepatic impairment.[31] However, administration of trifluridine/tipiracil is not recommended in patients with baseline moderate or severe hepatic impairment (total bilirubin >1.5× ULN) as a higher incidence of grade 3/4 hyperbilirubinaemia has been observed in patients with baseline moderate hepatic impairment.

When considering the timeframe for potential tolerability/safety issues, the main adverse events with regorafenib peaked during the first two cycles of treatment in CORRECT, tapering to a relatively stable lower incidence over later cycles, suggesting the main focus of safety monitoring should be during this initial cycle.[32] A dose-escalation 'upstep' approach for regorafenib, which starts with an initial 80–120 mg dose, can allow toxicity in a patient to be monitored before gradually moving up to the standard 160 mg dose.[28 33] In RECOURSE, 14% of patients receiving trifluridine/tipiracil required dose reductions and 53% of patients required dose delays,[12] while in CORRECT 38% of patients receiving regorafenib required a dose reduction and 61% required a dose interruption.[11] Alternative approaches to dosing with regorafenib (ReDOS), starting with an 80 mg/day dose with weekly dose escalation up to the standard 160 mg/day dose, have demonstrated an improvement in some toxicities.[28 33] Other trials exploring alternative flexible dosing approaches, such as the REARRANGE study (NCT02835924), will confirm whether this approach could improve regorafenib risk/benefit.

Analyses of patient well-being and QoL in later line treatment of mCRC

QoL remains an important issue for patients with cancer, since it is affected by both the disease and treatments received.[23] Thus, physicians need to consider balancing any extended survival with the likely quality of this extended life. There was no formal assessment of QoL in the original RECOURSE publication, although the study did demonstrate that trifluridine/tipiracil was associated with a significant delay in worsening of ECOG PS from a baseline of 0–1 to ≥2 versus placebo.[1223] Subsequent analysis of RECOURSE has demonstrated that trifluridine/tipiracil confers a clinically meaningful improvement in quality survival time.[34] QoL has been prospectively analysed in CORRECT and CONCUR, with no differences reported between the regorafenib and placebo groups in time to deterioration of QoL and health status, although ECOG PS was not investigated for regorafenib.[11 27]

STRATEGIES FOR EFFECTIVE PATIENT MANAGEMENT

The importance of effective physician–patient communication

Successful communication between physicians and patients promotes greater patient satisfaction with medical care, which in turn fosters higher levels of adherence, a particularly important goal when using oral treatments.[35] In addition, treatment-related adverse events can affect willingness, adherence to treatment and QoL. In later lines of therapy, adverse events can also have more impact on physical and mental function. Thus, effective communication regarding potential adverse events and subsequent management strategies remains essential in patients with mCRC.

Oral chemotherapy typically involves fewer required visits to the clinic than with intravenous chemotherapy, providing a reduced number of opportunities for patient education, counselling and communication.[36] Therefore, effective physician–patient discussion of which adverse events to expect and how to react to these before the initiation of oral trifluridine/tipiracil or regorafenib should be seen to be a critical step in supporting patient adherence to treatment.

Factors affecting adherence

Non-adherence to treatment increases patients' risk profile and compromises treatment outcomes.[35] Thus, it is important for patient adherence, along with any disease-associated symptoms or adverse effects which may impact on this, to be closely monitored at each visit

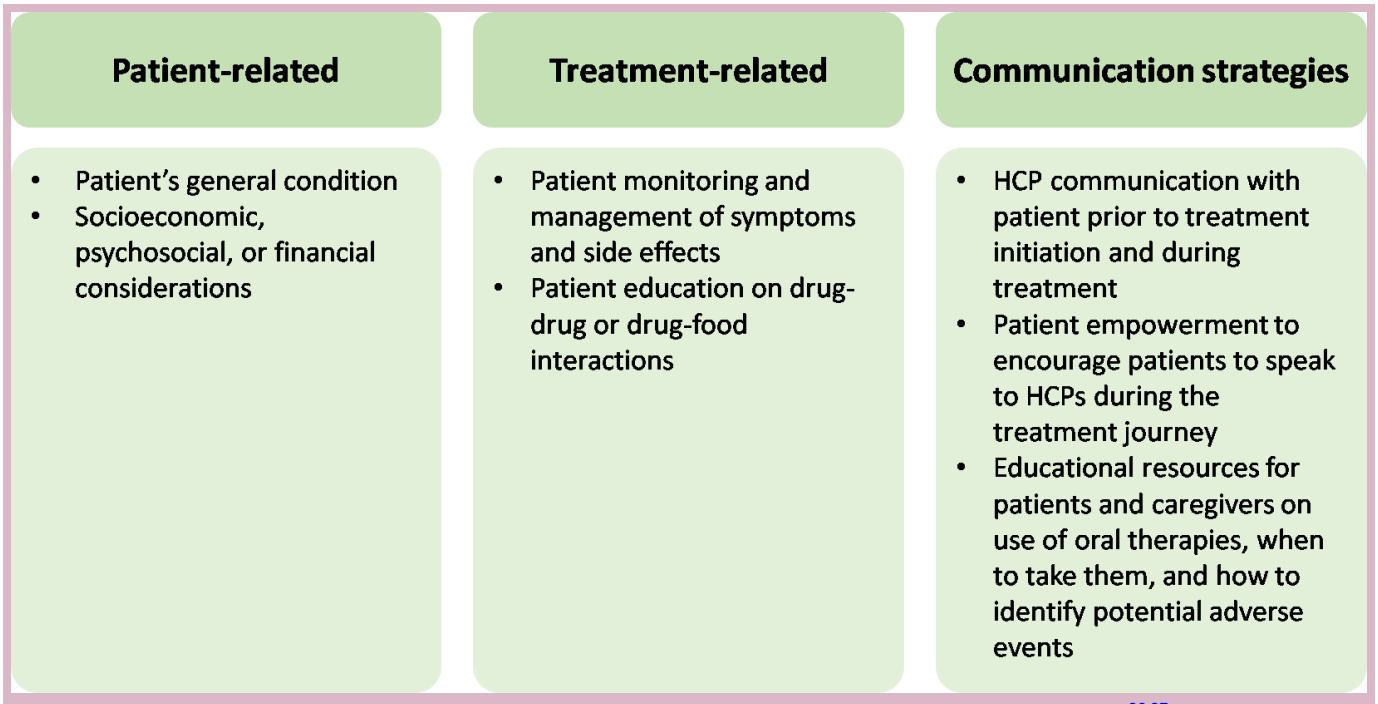

Figure 2 Factors affecting patient adherence to third-line oral therapies in metastatic colorectal cancer.[36 37] HCP, healthcare professional.

to the clinic. Factors affecting adherence can generally be split into patient-related factors and treatment-related factors. Patient-related factors include the patient's general condition, along with socioeconomic, psychosocial and financial considerations, while treatment-related factors include patient monitoring and management of symptoms and side effects, and patient education[35–37] (figure 2). A prospective, multicentre, real-life observational cohort Italian study has previously demonstrated that patients' level of education, concomitant other oral medications and patients' general clinical condition may influence adherence to regorafenib.[37]

An important factor influencing adherence is the effective management of symptoms and/or side effects of therapy.[36] As previously mentioned, trifluridine/tipiracil is associated with haematological adverse events, such as neutropaenia, while non-haematological adverse events such as HFSR are typically reported with regorafenib.[11 12]

Regorafenib and HFSR

In HFSR associated with regorafenib use, patients initially describe a sensation developing from tingling to burning over a few days (prodromal phase of dysesthesia), before developing bilateral, painful, sharply demarcated, asymmetric erythema, and large, tense blisters which evolve into callus-like hyperkeratosis.[38] HFSR symptoms typically occur at pressure-bearing points, such as the soles of the feet (particularly the heel area), palms of the hands and elbows, and can be troublesome for patients, affecting their ability to carry out everyday activities and get on with their lives. It is therefore important that physicians regularly monitor for, identify and manage symptoms of HFSR at an early stage to reduce the impact that this adverse event may have on treatment adherence. The main goals of HFSR management are to reduce the risk of it developing and alleviate the symptoms of established HFSR[38]; the skin should be kept well hydrated with a thick urea-based cream, calluses should regularly removed, and pain medication used, as needed. Alternative approaches to dosing with regorafenib, as investigated in ReDOS (80 mg/day dose with weekly dose escalation up to the standard 160 mg/day dose), suggest that a reduced starting dose can result in fewer subjective complaints about adverse events such as HFSR.[28 33]

Trifluridine/tipiracil and neutropaenia

Myelosuppression is one of the main adverse events observed with trifluridine/tipiracil, although neutropaenia associated with trifluridine/tipiracil remains a manageable treatment-related toxicity.[36] Physicians should use caution when considering dose reductions of trifluridine/tipiracil in patients who present with mild neutropaenia, where it may be more prudent to delay treatment rather than reduce the dose to minimise any negative impact on clinical efficacy. Importantly, some data suggest that neutropaenia may be a positive predictive factor for trifluridine/tipiracil efficacy, and an association between occurrence of earliest onset of grade 3/4 neutropaenia and survival benefit has been reported.[39 40] It is also important to note that grade ≥3 neutropaenia can occur for the first time after the first cycle of trifluridine/tipiracil, as reported in RECOURSE.[12] Available dosing information stipulates that all patients require a complete blood count prior to receiving trifluridine/tipiracil and that this should be maintained on day 15 of each subsequent 28-day cycle.[41] In the event of grade 4 neutropaenia

(defined as an absolute neutrophil count [ANC] <500/mm^3) within a treatment cycle, the dose of trifluridine/tipiracil should be held until the ANC increases to ≥1500/mm^3. If this treatment delay takes longer than 1 week, it is advised that the dose of trifluridine/tipiracil in the next cycle should be reduced by 5 mg/m^2 per dose from the previous dosing level. In the event of febrile neutropaenia, the dose of trifluridine/tipiracil should be held until the current episode is completely resolved, with the drug dose in the subsequent cycle being reduced by 5 mg/m^2 per dose from the previous dosing level.

Current NCCN and ESMO guidelines recommend the use of prophylactic myeloid growth factors to prevent the development of febrile neutropaenia in patients who receive myelosuppressive chemotherapy.[4 23] Of note, 9.4% of patients in RECOURSE received granulocyte colony-stimulating factor support.[12] However, prophylactic use is not recommended in combination with trifluridine/tipiracil.

CONCLUSIONS

Based on available efficacy data, treatment with either trifluridine/tipiracil or regorafenib is an appropriate first choice beyond second-line therapy to support improvements in OS in patients with mCRC. As there is no available evidence to suggest better efficacy for either treatment in this patient population, key determinants of therapy choice will likely include safety/tolerability profiles, patient PS and treatment-associated QoL. Given the lack of biomarkers of response to both drugs, it has been suggested that the toxicity profile of trifluridine/tipiracil may result in better acceptance by the oncological community compared with regorafenib[43]: the indirect comparison confirmed an increased risk of grade ≥3 adverse events for regorafenib versus trifluridine/tipiracil.[11 12 27 44 45] However, toxicity mitigation strategies are available for regorafenib, with ReDOS suggesting that the initiation of a low starting dose and subsequent incremental dosing may lead to lower toxicity, thus positively impacting on QoL and potentially treatment outcome.

The early identification and effective management of adverse events in patients receiving trifluridine/tipiracil or regorafenib remain important. In addition, effective physician–patient communication is an essential element in addressing these and other general side effects such as nausea, vomiting and fatigue, along with treatment expectations. Such strategies are critical because they might help patients continue therapy for a longer time, greatly facilitate patient adherence to therapy, and ultimately improve patients' QoL and eventual clinical outcomes. It is also important to highlight the need for thorough patient follow-up to maximise patient outcomes in the mCRC refractory setting, with the possibility that a second physician opinion may be necessary.

In summary, the use of trifluridine/tipiracil or regorafenib beyond second line for chemorefractory mCRC can improve patient OS. However, due to the narrow risk to benefit ratio when compared with earlier lines of therapy, considerable physician expertise is needed to enable appropriate treatment selection.

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