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How Quality of Life Can Inform Management Decisions in Later-Line Metastatic Colorectal Cancer

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Abstract: For many years, the focus of treatment in patients with metastatic colorectal cancer has been to prolong patient survival. Increasing evidence, however, highlights the quality-of-life issues these patients face as they progress through lines of treatment. Quality of life is important to patients with metastatic colorectal cancer, and can greatly impact their overall well-being. Some studies have found associations between quality of life and survival. The approval by the US Food and Drug Administration of regorafenib and trifluridine/tipiracil in the third-line setting for patients with metastatic disease provided an option for salvage therapy that improved overall survival in heavily pretreated patients. The safety profile of each agent can help guide selection. Patients with metastatic colorectal cancer require an individualized treatment strategy that incorporates their age, comorbidities, and prior treatments. New data on quality-of-life measures from pivotal clinical trials also provide insight into selection of treatment. These factors should be considered along with the patient's preferences and individual treatment goals.

Quality-of-Life Concerns in Patients With Metastatic Colorectal Cancer

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Overall, quality-of-life data for patients with metastatic colorectal cancer (mCRC) are limited, particularly in the third-line treatment setting. Systematic reviews have provided some insights. A systematic review of primary publications published between 2012 and 2018 evaluated quality-of-life assessment and reporting among phase 3 clinical trials in patients with colorectal cancer.[1] Among the 67 publications identified, 41 (61.2%) lacked quality-of-life endpoints. For the remaining 26 publications in which quality of life was listed as an endpoint, results were not reported in 10 (38.5%). Overall, the authors of this review determined that no quality-of-life data were available in 76.1% of the primary analysis publications. Importantly, of the 47 studies conducted in patients with metastatic disease, 32 (68.1%) did not include quality-of-life data.

Another systematic review focused on the link between severe toxicity and global quality of life in patients with mCRC.[2] In this review, the authors examined whether newer agents that improve overall survival are associated with decreased quality of life. The review included phase 3 trials, published between 2004 and 2016, that evaluated systemic palliative treatments in patients with mCRC. Interestingly, the authors found no difference in global quality of life among patients in the experimental arms vs the control arms in 25 of the 30 trials (83%), although 22 of these trials (73%) reported increased toxicity in the experimental arms (Figure 1).[2] Even among the 22 trials that showed increased toxicity, quality-of-life outcomes remained unaffected or improved in 19 trials (86%). Therefore, the authors found that although there was typically higher toxicity in the experimental arms across a majority of the randomized trials, this increase did not affect the global quality-of-life outcomes. These data are similar to those reported for regorafenib and trifluridine/tipiracil in trials of patients with mCRC.[4,5] The patients enrolled in these trials were heavily pretreated and had high disease-related symptom burden, which may partly explain why quality-of-life outcomes were not decreased in the experimental arms. Another reason may be that the trials used quality-of-life scales that lacked the sensitivity to recognize certain adverse events related not only to physical well-being, but also social functioning and financial toxicity.

Impact of Patient Demographics and Characteristics on Quality of Life

When examining quality of life in patients with heavily pretreated mCRC, it is helpful to consider patient demographics. In the third-line setting, the best measure of demographics is provided by randomized trials, such as the pivotal phase 3 CORRECT trial of regorafenib; the pivotal phase 3 RECOURSE trial of trifluridine/tipiracil; and the phase 3 IMblaze370 trial, in which regorafenib, as the control treatment, was compared with atezolizumab administered with or without cobimetinib.[4-6] A caveat is that study populations may not always represent the real-

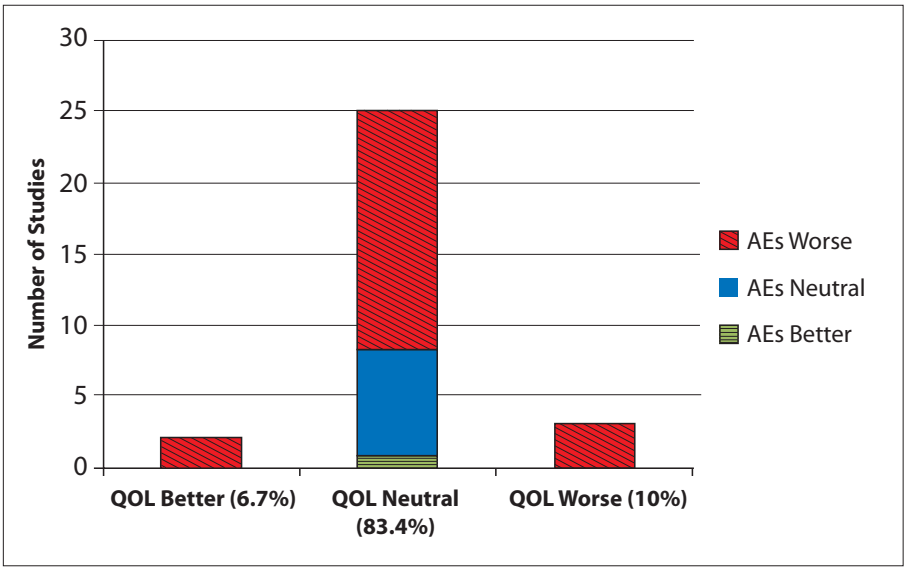

Figure 1. Global quality of life and toxicity in a systematic review of trials evaluating treatments for patients with metastatic colorectal cancer. Data pooled from 30 trials are shown. AEs, adverse events; QOL, quality of life. Adapted from Schuurhuizen CSEW et al. *Ann Oncol.* 2017;28(3):478-486.[2]

world population. However, patient demographic factors can affect quality of life, especially in the third-line setting.

One of the most obvious demographics that can impact quality of life is the patient's age. Across these 3 trials, the median age of the study population was between 59 and 63 years.[4-6] In the CORRECT trial, the patient age ranged from 54 to 68 years, with a median age of approximately 61 years.[5] The RECOURSE trial enrolled patients ages 27 to 82 years, with a median age of approximately 63 years.[4] In the IMblaze370 study, the age range was 51 to 67 years, with a median age of 56 to 59 years.[6] The patients in these trials were slightly younger than those presenting for third-line treatment in the clinic.

These trials enrolled slightly more men than women, at a ratio of approximately 60% to 40%.[4-6] Although there are some caveats concerning how sex and racial biases can impact enrollment in clinical trials, this ratio is generally reflective of the overall population.

Interestingly, between 50% to 60% of patients enrolled in these trials had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and approximately 40% had an ECOG performance status of 1.[4-6] Most of the patients had received 3 or more lines of treatment. This finding raises a clinical situation unique to mCRC compared with gastric, pancreatic, or biliary tract cancers: most patients with mCRC are able to preserve their performance status through the third or fourth line of treatment.

Certain patient characteristics unmistakably lead to quality-of-life issues. These patients are heavily pretreated. The median progression-free survival is approximately 9 to 12 months for first-line treatment and 6 to 7 months for second-line treatment. During this time, patients receive combination chemotherapy regimens, plus a biologic therapy (either anti–vascular endothelial growth factor [VEGF] or anti–epidermal growth factor receptor [EGFR] agents). As a result, when these patients initiate third-line treatment, they are likely to have significant bone marrow toxicity, organ toxicity, and skin toxicity. It is understandable that these patients might have unique treatment-related and psychosocial burdens.

There are other characteristics that may affect quality of life for patients with mCRC in the third-line setting. Surgery is a common treatment for patients with colorectal cancer, even for those with metastatic disease, or patients may have received local therapies. For instance, in patients who may have undergone a colostomy or peritoneal surgery with bowel resection, certain quality-of-life issues centered around bowel movements may arise. Whether the primary tumor is intact or has been removed can also affect quality of life. Subacute or acute partial bowel obstructions have been reported in patients with peritoneal disease, which can exacerbate gastrointestinal symptoms and amplify quality-of-life issues with therapy.

The overall symptom burden arising from the sites and extent of metastases is another aspect that can impact quality of life. Patients who present with peritoneal-predominant disease tend to have a poor quality of life.[7] In contrast, patients who present with lung-only metastases have a different set of symptoms and tend to have a better quality of life owing to relatively indolent and small-volume disease until later stages.

Financial Toxicity

A critical aspect to quality of life is the patient's financial burden. In my own practice, financial concerns have assumed a prominent role for patients. Data in diverse

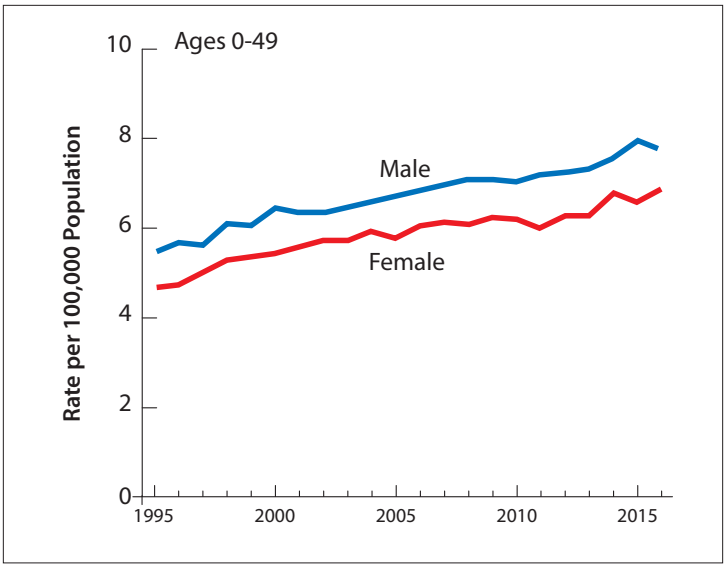

Figure 2. Colorectal cancer incidence among younger patients in the United States from 1995 to 2016. Trends were assessed by the American Cancer Society, based on data from the North American Association of Central Cancer Registries, 2019. The rates are age-adjusted to the 2000 US standard population. The incidence rates are adjusted for reporting delays and exclude data from the appendix. Adapted from American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf.[11]

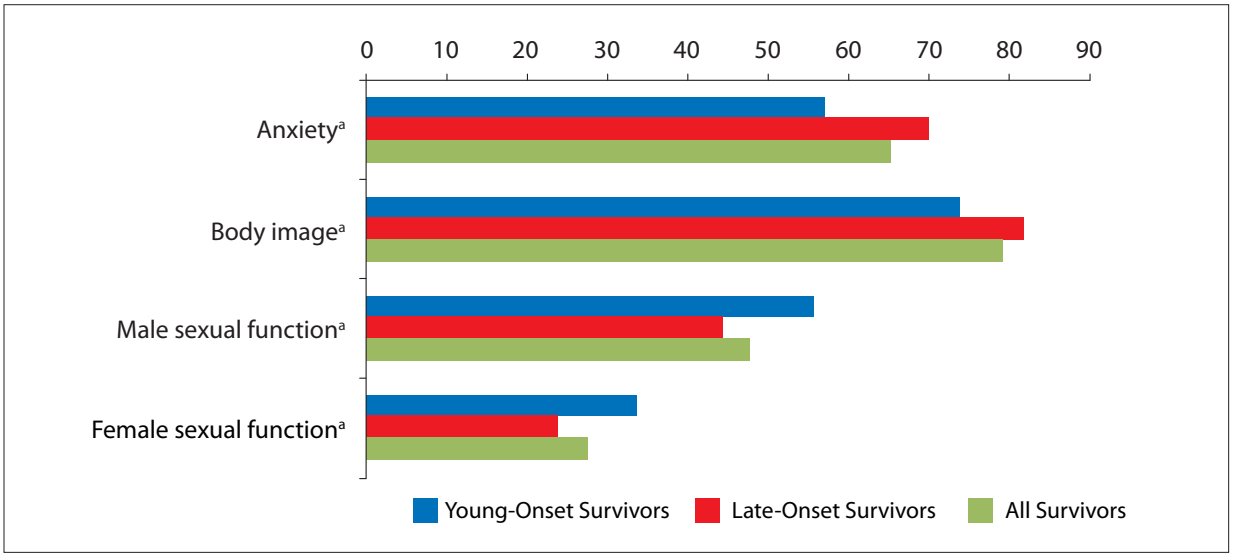

Figure 3. Functional domain scores among patients with colorectal cancer according to time of onset of the disease. Scores were assessed with the EORTC CR29. A higher score indicates better functioning. EORTC CR29, European Organisation for Research and Treatment of Cancer Colorectal Cancer module. [a]*P*<.05. Adapted from Bailey CE et al. *J Gastrointest Surg*. 2015;19(1):180-188.[12]

cancers support the notion that financial burdens can adversely affect quality of life.[8] It seems likely that these observations are also true for heavily pretreated patients with mCRC. A study presented at the 2020 American Society of Clinical Oncology Quality Care Symposium reported that major financial hardship accumulated over time for patients diagnosed with mCRC enrolled in the SWOG S1417CD study.[9] Almost 75% of these patients reported major financial hardship at 12 months, despite having access to health insurance. The costs associated with treatment can place a significant burden on patients and their loved ones.

Quality-of-Life Issues in Younger Patients

Younger adults with mCRC present a unique set of quality-of-life issues. The incidence of colorectal cancer is rising in this population (Figure 2).[10,11] Younger patients tend to have a worse prognosis compared with the more traditional, slightly older mCRC population. This phenomenon could be linked to the underlying biology of the disease, as well as other social and financial aspects. For example, it is not uncommon for younger adult patients with mCRC to lack health insurance. Many of these younger patients become lost to follow-up or do not

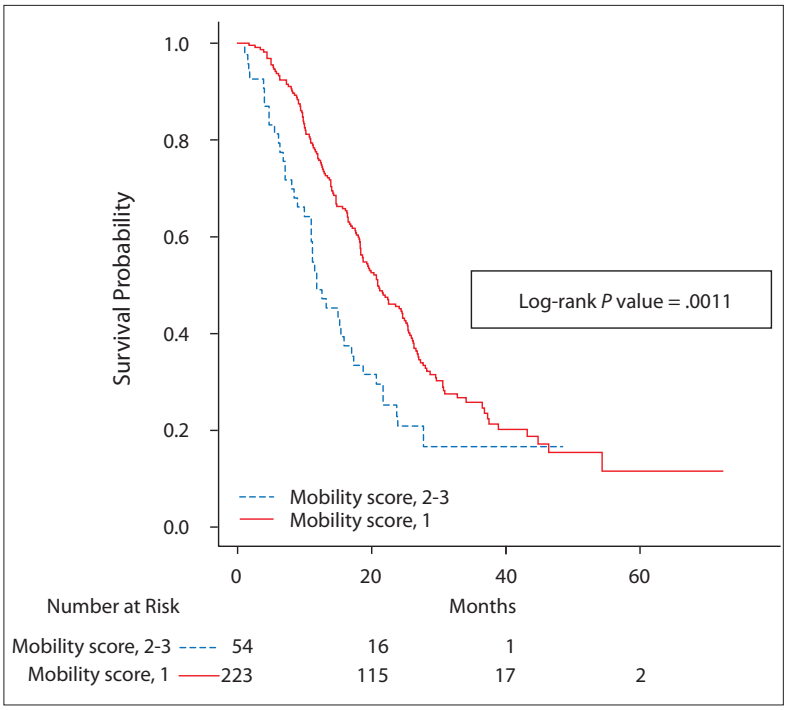

Figure 4. Overall survival among patients with colorectal cancer according to their mobility in the phase 3 GERCOR OPTIMOX1 study. Patients without mobility problems received a score of 1. Those with mobility problems received a score of 2 or 3. Adapted from Diouf M et al. *Health Qual Life Outcomes*. 2014;12:69.[13]

regularly return for treatment, which might reflect issues related to insurance or finances. Additionally, a diagnosis of colorectal cancer is associated with a great deal of anxiety and apprehension, which might be particularly heightened in younger patients (Figure 3).[12]

Associations Between Quality of Life and Mortality

Among patients with mCRC, there are no robust examples in which quality of life has been directly linked with patient survival. However, this association seems to make sense. An analysis from the GERCOR OPTIMOX1 study showed that quality of life was associated with more symptom burden and potentially poorer overall survival.[13] This phase 3 trial compared 2 strategies of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) chemotherapy in patients with previously untreated mCRC. A subsequent analysis evaluated the independent prognostic value of quality of life on overall survival, finding that both mobility (Figure 4) and pain dimensions of quality of life are independent prognostic factors. For example, the median overall survival was 20.9 months for patients without mobility-related quality-of-life issues vs 11.8 months for patients with mobility-related quality-of-life issues (log-rank *P*=.0011).

Studies of regorafenib and trifluridine/tipiracil in the third-line setting appear to show that although these agents are associated with some toxicity, they do not contribute to a significant deterioration in quality of life.[4,5] This observation may reflect inadequacies in the tools chosen to measure quality of life. An important unmet need in mCRC is for well-designed, validated, and established quality-of-life measurement tools.

Disclosure

Dr Raghav has no real or apparent conflicts of interest to report.

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Recent Quality-of-Life Data in Patients With Metastatic Colorectal Cancer

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For some time, there has been a push to incorporate greater quality-of-life measures in phase 3 trials of mCRC.[1] There are multiple well-validated platforms for measuring health-related quality of life (HRQOL) as a patient-reported outcome (PRO), which are being integrated into studies. Quality-of-life data are primarily drawn from randomized trials. It can be challenging to assess the quality of single-arm studies, owing to selection bias. Several recent trials in colon cancer, as well as other gastrointestinal malignancies, have included quality-of-life data. The incorporation of these measures into clinical trial design is now the norm.

One notable example of impactful incorporation of quality-of-life data is the BEACON trial, which enrolled patients with metastatic colorectal cancer that harbors a *BRAF* mutation. The *BRAF* V600E mutation is associated with adverse outcomes leading to significant symptoms and burdensome disease.[2] The BEACON trial was a global, randomized, open-label, 3-arm phase 3 study comparing the triplet regimen of encorafenib,

Table 1. Rates of HFSR, as Per the CTCAE, Among Patients Treated With Regorafenib in the ReDOS Trial[8,9]

	Cycle 1 Regorafenib			Cycle 2 Regorafenib		
HFSR Outcome	**Preemptive Clobetasol (n=61)**	**Reactive Clobetasol (n=55)**	***P* Value**	**Preemptive Clobetasol (n=61)**	**Reactive Clobetasol (n=55)**	***P* Value**
No HFSR	33 (54)	25 (45)	.35	20 (33)	8 (15)	.02
Any HFSR[a]	28 (46)	30 (55)		41 (67)	47 (85)	
HFSR by grade						
0	33 (54)	25 (45)	.35	20 (33)	8 (15)	.12
1	11 (18)	8 (15)		18 (30)	18 (43)	
2	11 (18)	13 (24)		5 (8)	10 (18)	
3	6 (10)	6 (11)		2 (3)	4 (7)	
Missing	0 (0)	3 (5)		16 (26)[b]	15 (27)[b]	

Data are presented as n (%).
[a]This row includes all patients with hand-foot skin reaction, as well as patients with missing data.
[b]By cycle 2, 28 patients had stopped regorafenib, resulting in missing data.
CTCAE, Common Terminology for Adverse Events; HFSR, hand-foot skin reaction.
Adapted from Jatoi A et al. *Oncologist*. 2021;26(7):610-618.[9]

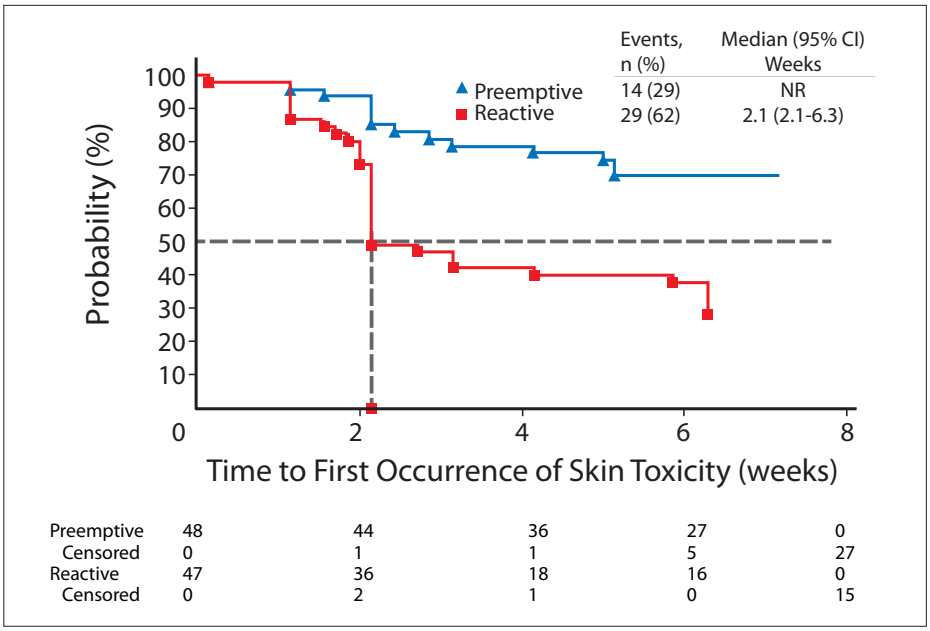

Figure 5. The time to first occurrence of a specific grade 2 or higher skin toxicity in an analysis of the phase 2 STEPP study, which evaluated the impact of a preemptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. NR, not reached. Adapted from Lacouture ME et al. *J Clin Oncol*. 2010;28(8):1351-1357.[7]

binimetinib, and cetuximab or the doublet of encorafenib and cetuximab vs the control treatment of irinotecan plus cetuximab or folinic acid, 5-fluorouracil, and irinotecan (FOLFIRI) plus cetuximab in patients with colon cancer and the *BRAF* V600E mutation. Quality-of-life data were assessed as a secondary endpoint and included the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30), the Functional Assessment of Cancer Therapy Colon Cancer (FACT-C), the EuroQol 5D 5L, and the Patient Global Impression of Change (PGIC).

The triplet and doublet regimens showed a clear reduction in the risk of quality-of-life deterioration compared with the control regimen.[3] The QLQ-C30 showed a reduction in the risk of quality-of-life deterioration of 45% (hazard ratio [HR], 0.55; 95% CI, 0.43-0.70) for the triplet regimen and 46% (HR, 0.54; 95% CI, 0.43-0.69) for the doublet regimen vs the control. The FACT-C also showed a favorable decrease in risk reduction of quality of life of 44% (HR, 0.56; 95% CI, 0.44-0.71) for the triplet and 43% (HR, 0.57; 95% CI, 0.45-0.72) for the doublet compared with the control. The EuroQol 5D 5L and PGIC assessments produced similar results.

The open-label, randomized phase 3 KEYNOTE-177 trial compared quality of life in patients with microsatellite instability–high (MSI-H) or mismatch repair–deficient metastatic colorectal cancer.[4] The quality-of-life analysis included 152 patients treated with pembrolizumab and 142 treated with chemotherapy. At week 18, least squares mean change in EORTC QLQ-C30 global health status/quality-of-life scores were improved with pembrolizumab vs chemotherapy (between-group least squares mean difference, 8.96; 95% CI, 4.24-13.69; 2-sided nominal *P*=.0002). Furthermore, the median time to deterioration was longer with pembrolizumab compared with chemotherapy for global health status/quality of life (HR, 0.61; 95% CI, 0.38-0.98; 1-sided nominal *P*=.019).

Measures to Address Treatment-Related Toxicity

Researchers have also focused on mitigating measures for patients who receive treatments associated with toxicities that can affect the gastrointestinal system as well as the skin, to address adverse events such as hand-foot skin reaction and acneiform rash. Studies have evaluated the use of minocycline preemptively before the administration of EGFR inhibitors.[5,6] A randomized, double-blind trial examined the use of prophylactic oral minocycline for the prevention of cetuximab-related acneiform rash by assigning patients to receive daily oral minocycline (n=24) or placebo (n=24) starting on day 1 of cetuximab therapy. Patients receiving minocycline were less likely to report moderate to severe itch at week 4 (20% vs 50%; *P*=.05).[6]

Preemptive treatment with minocycline has also been examined among patients treated with panitumumab. The phase 2, open-label, randomized STEPP trial assessed the impact of a preemptive skin treatment regimen on skin toxicities and quality of life in patients with mCRC.[7] In this study, patients receiving panitumumab were randomly assigned to a preemptive vs a reactive treatment for skin toxicity. More than twice as many patients in the reactive treatment group developed grade 2 or higher skin toxicities during the 6-week skin treatment period as

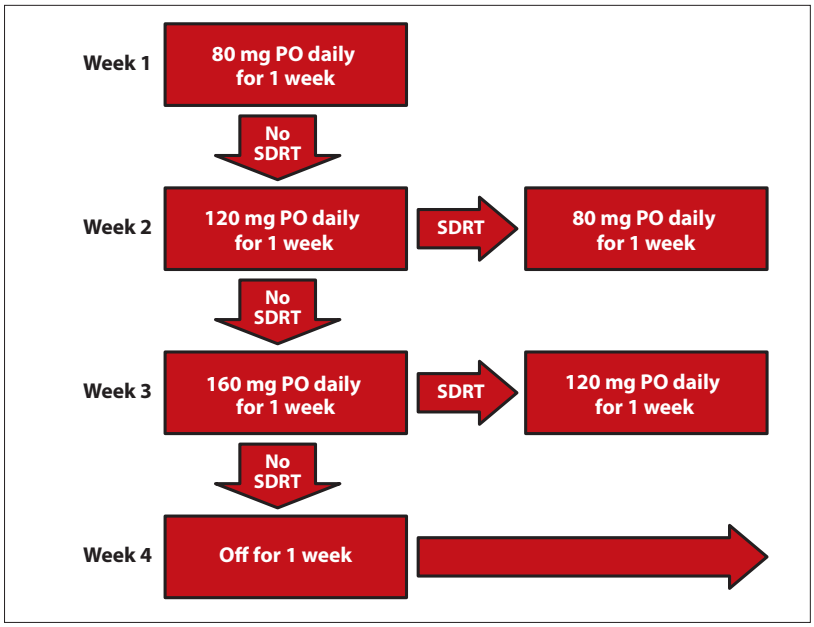

Figure 6. An incremental dose-escalation protocol for administration of regorafenib. PO, by mouth; SDRT, significant drug-related toxicities. Reprinted from Grothey A. *Clin Adv Hematol Oncol.* 2016;14(suppl 3):8-10.[14]

compared with patients in the preemptive group (62% vs 29%; Figure 5). This study also examined the impact of preemptive vs reactive treatment on quality of life, as measured by the mean change in the Dermatology Life Quality Index score from baseline to week 3. The mean change was 1.3 points in the preemptive group, but decreased by 4.2 points in the reactive group.

The randomized, multicenter, open-label phase 2 ReDOS study compared a dose-escalated regimen of regorafenib vs the standard 160 mg regimen (Figure 6).[8] A preplanned analysis of the ReDOS trial examined the use of a corticosteroid cream, clobetasol, applied preemptively or reactively to mitigate hand-foot skin reaction in patients treated with regorafenib.[9] Throughout the first 2 cycles, no evidence of hand-foot skin reaction was reported in 30% of patients who received clobetasol preemptively (n=61) vs 13% of those who received clobetasol reactively (n=55; *P*=.03; Table 1). No adverse events owing to clobetasol were reported. Patient-reported outcomes showed that hand-foot skin reaction affected nearly all activities of daily living. Quality of life was improved in patients who received preemptive vs reactive clobetasol. This analysis therefore showed that preemptive measures can improve quality of life among patients treated with agents such as regorafenib, cetuximab, and panitumumab.

The ReDOS trial integrated an extensive quality-of-life component.[8] The study had 4 arms, consisting of patients assigned to regorafenib dose escalation with preemptive (n=29) or reactive (n=27) clobetasol or regorafenib at the standard dose with preemptive (n=34) or reactive clobetasol (n=33). Quality of life between the groups was measured by the HFS-14 questionnaire, which measured hand-foot syndrome; the Brief Fatigue Inventory; and the Longitudinal Aging Study Amsterdam (LASA) physical activity questionnaire. At week 2 of treatment, the mean quality-of-life scores as determined by the Brief Fatigue Inventory questionnaire were significantly better in the dose-escalation group compared with the standard-dose group (5.30 vs 4.25; *P*=.046). Specific measures included interference with general activity (5.59 vs 4.31; *P*=.032), mood (6.22 vs 4.92; *P*=.038), walking ability (5.96 vs 4.50; *P*=.019), and normal work (5.48 vs 4.17; *P*=.039). No difference in quality-of-life scores was found between the dosing strategies at weeks 4, 6, and 8. These data show that the dose-escalation strategy allows quality of life to be maintained early in treatment. They also illustrate how quality-of-life measures can help optimize strategies that will help patients tolerate the therapies they receive throughout the course of treatment.

The focus on quality of life must also include ways to delay deterioration of HRQOL. Several studies of regorafenib in multiple tumor types have measured time until definitive deterioration, defined as the patient's first minimal clinically important deterioration in HRQOL from baseline that did not resolve.[10] A pooled analysis of data from studies of patients with mCRC (the CORRECT and CONCUR trials), advanced gastrointestinal stromal tumor (the GRID trial), and hepatocellular carcinoma (the RESORCE study) showed that regorafenib significantly delayed time until definitive deterioration as compared with placebo.[10]

A prospective, cross-sectional, noninterventional study examined patient-reported quality-of-life benefits of trifluridine/tipiracil compared with best supportive

care in patients with refractory mCRC.[11] Among the 105 patients included in the trial (50 in the trifluridine/tipiracil arm and 55 in the control arm), patients treated with trifluridine/tipiracil reported lower physical distress (*P*=.0042), lower psychological distress (*P*<.0001), lower activity impairment (*P*<.0001), and better overall valuation of life (*P*<.0001). Although this study did not track changes in baseline for patient-reported quality of life, it does make a clear case for improved quality of life in patients treated with trifluridine/tipiracil compared with best supportive care.

There are several mitigating strategies in use. Maintenance strategies, early discontinuation, shift to maintenance, and drug holidays might be options to offer some patients. As an example, say a patient is receiving treatment with FOLFOX; FOLFIRI; or fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX). After 3 to 4 months, he or she has a good response or even stable disease. At this point, it can be helpful to discuss and compare the value and implications of further treatment vs maintenance or even a drug holiday. Some patients wish to stop treatment completely. The data clearly show that when treatment lasts until disease progression or toxicity, efficacy is not necessarily improved and toxicity levels may be high.[12] Treatments such as oxaliplatin and irinotecan can induce neuropathy, significant fatigue, and chronic diarrhea.[12,13] Treatment breaks or maintenance therapies can help patients accept long-term therapy and improve their quality of life. The discussion with the patient should always balance goals regarding survival vs toxicity. Prolonging survival is important. However, for the vast majority of patients with mCRC, the primary goal of systemic therapy is palliative.

Quality of life can mean different things for different patients. In clinical trials, quality-of-life measures integrate factors tied to emotional well-being, physical well-being, relationships, and physical functionality. All of these factors are important and should be raised during discussions with the patient. It is necessary to consider the patient's goals. Are they thinking about a vacation? Are they trying to spend more time with family? Is it the right time to take a break? Is it the right time to transition to maintenance therapy? Clinicians must balance assessment of toxicities throughout the continuum of treatment with the patient's goals to best address quality-of-life issues.

The number of long-term survivors is increasing. Among patients with metastatic colon cancer, almost half are alive 5 years after diagnosis. In comparison, 20 years ago, only 10% or 20% of patients survived beyond 5 years. Most patients, however, will need to receive treatment for the rest of their life. Only 30% to 40% of patients are cured by first-line treatment. The overwhelming majority of the other patients will require some form of treatment for the rest of their lives. Treatment has become a marathon, rather than a sprint. Clinicians cannot just focus on the most aggressive therapy. There must be a measured approach that includes palliation. Clinicians should learn what is acceptable to each patient. Treatment breaks, maintenance, proper targets, and preemptive measures should be considered, when indicated. Patients and their families should be considered partners in the journey.

Disclosure

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Quality-of-Life Factors Impacting Selection of Third-Line Treatment in Metastatic Colorectal Cancer

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The management of quality of life is an important challenge in patients with mCRC. As an example, I was recently speaking with a patient who is responding well, after 4 months of frontline therapy. Peripheral neuropathy arising from oxaliplatin is starting to affect his quality of life, and he asked why more attention is not given to this adverse event. Oncologists tend to focus on progression-free survival and response rate. However, there are other significant issues that greatly impact a patient's quality of life. This patient's question is a relevant one. There should be better strategies to manage peripheral neuropathy and other adverse events. Clinicians must remain mindful of a patient's quality of life during every interaction.

Dosing Strategies to Improve Quality of Life

The IDEA collaboration trial evaluated six phase 3 studies of patients with nonmetastatic stage 3 colon cancer.[1] The final pooled analysis suggested that in the adjuvant setting in patients with stage 3 disease, there is a potential to diminish the intensity of chemotherapy without jeopardizing efficacy. This analysis did not show noninferiority in overall survival for 3 vs 6 months of adjuvant chemotherapy. However, the absolute difference in 5-year overall survival (a prespecified secondary endpoint) was approximately 0.4%. When placed in a clinical context, this small difference supports the use of 3 months of adjuvant capecitabine and oxaliplatin (CAPOX) for most patients with stage 3 colon cancer. The shorter treatment regimen will reduce toxicities, inconveniencies to the patients, and cost.

In metastatic disease, the ReDOS trial of regorafenib aimed to improve quality of life through a dose-escalated strategy.[2] At the time of the study design, it was recognized that regorafenib conferred an overall survival benefit, even among heavily pretreated patients, per data from the phase 3 CORRECT and CONCUR trials (Figures 7 and 8).[3,4] This survival benefit, however, was associated with a possibility of significant toxicities and decreased quality of life. For example, in the pivotal phase 3 CORRECT trial, 67% of patients who received regorafenib required a dose modification owing to an adverse event, compared with 23% of patients in the placebo arm.[3] In both the CORRECT and the CONCUR studies, regorafenib was associated with a relatively high rate of toxicities (eg, fatigue, hand-foot skin reaction, hypertension, and diarrhea).[3,4] Therefore, the ReDOS study evaluated whether an alternative dose-escalation strategy would increase tolerability.[2]

A total of 123 patients with mCRC were randomly assigned to treatment with either the standard dosing

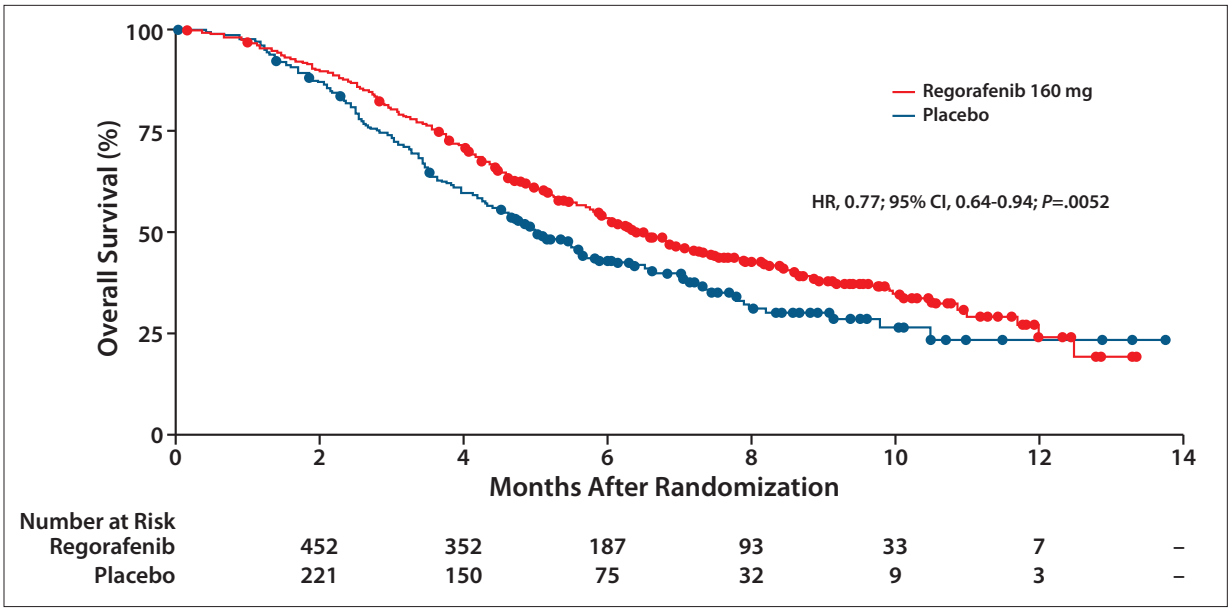

Figure 7. Median overall survival in the phase 3 CORRECT trial, which compared regorafenib vs placebo in patients with previously treated metastatic colorectal cancer. CORRECT, Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy. Adapted from Grothey A et al. *Lancet*. 2013;381(9863):303-312.[3]

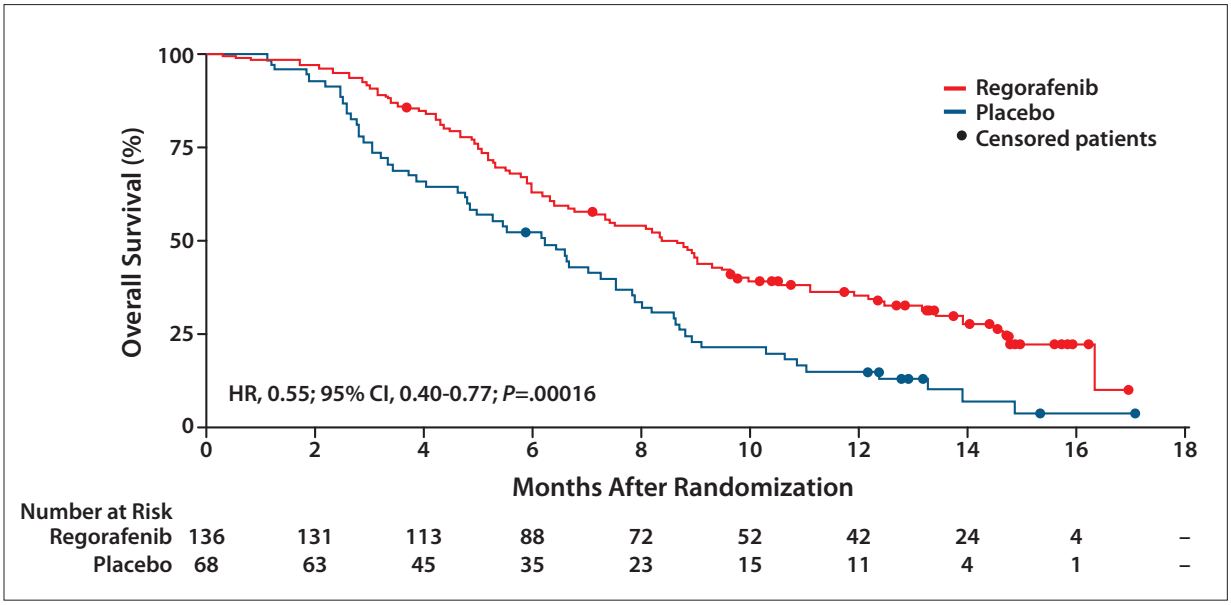

Figure 8. Median overall survival in the phase 3 CONCUR trial, which compared regorafenib plus best supportive care vs placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer. CONCUR, Patients With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy; HR, hazard ratio. Adapted from Li J et al. *Lancet Oncol*. 2015;16(6):619-629.[4]

regimen of regorafenib (160 mg once daily) or an alternative dosing strategy in which regorafenib was initiated at a dose of 80 mg once daily on days 1 to 7.[2] If the patient did not experience any significant drug-related toxicities, the dose of regorafenib was then escalated to 120 mg once daily on days 8 to 14, and then to 160 mg once daily on days 15 to 21. In cycle 2 and thereafter, patients subsequently received the highest tolerated dose from cycle 1. The primary endpoint was defined as the proportion of evaluable patients initiating cycle 3 of regorafenib.

Among the evaluable patients (n=116), the primary endpoint was achieved in 43% of patients in the dose-escalated arm, compared with 26% of patients in the standard-dosing arm (*P*=.043).[2] Overall survival was 9.8 months vs 6.0 months, respectively, but this difference did not reach statistical significance (HR, 0.72; 95% CI, 0.47-1.10; log-rank *P*=.12). Progression-free survival was similar between the arms (HR, 0.84; 95% CI, 0.57-1.24; log-rank *P*=.38).

The real impact of the dose-escalation strategy could be seen in the toxicity profiles of each arm.[2] During the first 2 treatment cycles, the rates of grade 3 adverse events commonly observed with regorafenib, including fatigue, hand-foot skin reaction, hypertension, and diarrhea, were lower in the dose-escalation group compared with the standard-dose group. The most common grade 3 or 4 adverse events reported were fatigue (13% in the dose-escalation arm vs 18% in the standard-dose arm), abdominal pain (17% vs 6%), hand-foot skin reaction (15% vs 16%), and hypertension (7% vs 15%). At baseline, quality of life (as measured the Brief Fatigue Inventory questionnaire) was similar between the arms. By the second week of treatment, the mean quality-of-life scores were significantly improved in the dose-escalation arm compared with the standard-dose arm. This improvement was observed across multiple quality-of-life indications, including current fatigue, general activity interference, mood interference, walking ability interference, and normal work interference. It should be noted that the quality-of-life scores did not significantly differ at weeks 4, 6, and 8.

The now widespread dissemination of the ReDOS strategies has greatly reinforced the notion in our community that there is a better way to dose these drugs that does not jeopardize efficacy. Gaining this understanding has been a critical step for clinicians to feel comfortable with these alternative dosing strategies. Interestingly, many clinicians were already prescribing regorafenib in a nonstandardized, dose-escalation strategy. This approach was then confirmed, reinforced, and standardized in the ReDOS study. Clinicians should be aware of the toxicity profile of regorafenib, in particular, hand-foot skin reaction and fatigue. Administration of regorafenib in a dose-escalated manner can allow patients to avoid these adverse events.

Quality-of-Life Discussions With Patients

When sequencing treatments, it is necessary to consider how the treatments can impact quality of life. Factors that help guide management choices include the patient's age and disease state, as well as characteristics of the agent. Additionally, most patients with mCRC—particularly those who have undergone prior surgeries—have gastrointestinal issues that can be difficult to manage. Among patients who have a history of multiple gastrointestinal surgeries, the impact of chemotherapy and associated morbidities worsens with time and each line of treatment. Additionally, among patients who are beginning third-line or later treatment, it is necessary to consider their previous treatments, which typically consist of FOLFOX and FOLFIRI regimens, plus biologic agents (either an anti-VEGF or an anti-EGFR therapy). Each of these treatments is associated with a unique toxicity profile leading to a specific set of side effects.

As patients develop progressive disease, the degree and depth of response—as well as the duration of progression-free survival—decrease with each line of therapy. Quality of life associated with the disease itself also tends to decrease.

Some of the large phase 3 studies with regorafenib in other malignancies have incorporated endpoints—often as a post hoc or exploratory analysis—to evaluate quality of life.[5,6] Often, it is measured using assessments such as the EORTC questionnaires. These endpoints are often referred to as time until definitive deterioration endpoints.[7]

My discussions with patients who are entering their third line of therapy begin by noting that it may not be necessary to initiate any further therapy. I then summarize the options that are approved by the US Food and Drug Administration (FDA) in this setting, as well as the pivotal trial data that supported these approvals. Some patients decide not to proceed with treatment based on concerns with pain or fatigue, and to avoid adverse events and further deterioration in quality of life. The FDA-approved agents—regorafenib and trifluridine/tipiracil—are not suitable for all patients.

When the patient decides to proceed with third-line therapy, the selection of treatment should be based on the expected efficacy and adverse events. In most cases, these patients have not already received treatment with a tyrosine kinase inhibitor, such as regorafenib. Toxicities associated with tyrosine kinase inhibitors are notably different from those associated with chemotherapy. Regorafenib may cause fatigue and hand-foot syndrome, rather than nausea, anemia, and neutropenia. Trifluridine/tipiracil may cause cytopenias and skin toxicity, which patients may have already experienced during previous lines of chemotherapy. In addition, some patients may be unfamiliar with taking a daily pill (unless they previously received capecitabine).

These considerations can help guide treatment selection and help ensure that the therapy matches the patient's particular needs. For example, if a patient developed long-term issues with thrombocytopenia or cytopenias in the

past, or if he or she does not want to undergo biweekly phlebotomies, then perhaps trifluridine/tipiracil is not the best option. For these patients, regorafenib would be a better choice. In contrast, if a patient developed significant fatigue or skin toxicities during prior lines of treatment, regorafenib might be avoided. Clearly, at the time of initiation of third-line therapy, performance status has deteriorated for almost all patients. This too will impact the choice of therapy. When we make these decisions, it is important to tailor the choice of the agent according to the known toxicity profile and the needs of the particular patient.

Disclosure

Dr Wainberg has received honoraria (directed to himself) from Amgen, AstraZeneca, Daiichi, Bayer, BMS, Merck, Ipsen, Five Prime, Gilead, Arcus, Astellas, Molecular Templates, and Array. He has been an advisor/consultant to Amgen, AstraZeneca, Daiichi, Bayer, BMS, Merck, Ipsen, Five Prime, Gilead, Arcus, Astellas, Molecular Templates, and Array. He has received research grants/funding (directed to his institution) from Amgen, AstraZeneca, Daiichi, Bayer, BMS, Merck, Ipsen, Five Prime, Gilead, Arcus, Astellas, Molecular Templates, Roche/Genentech, and Array/Pfizer.

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How Quality of Life Can Inform Management Decisions in Later-Line Metastatic Colorectal Cancer: Q&A

Tanios S. Bekaii-Saab, MD, Kanwal Raghav, MD, MBBS, and Zev A. Wainberg, MD

Tanios S. Bekaii-Saab, MD Are there any specific subgroups of patients that typically have a worse burden of disease, which likely would affect their quality of life?

Kanwal Raghav, MD, MBBS There are patients within certain molecular subgroups, such as *BRAF*-mutated, *HER2*-amplified, or MSI-high disease, who can be treated with targeted therapies rather than the standard of care. In MSI-high colorectal cancer, the treatment paradigm has shifted more toward the first-line setting. Patients with the *BRAF* mutation have a very high burden of aggressive disease, but can be successfully treated with BRAF-targeted therapies. In those cases where the response rates are very good, quality of life becomes less of a concern. When it is possible to improve the disease in a substantial manner, the deterioration in quality of life that might be associated with therapy-related toxicities is generally eclipsed by the improvement in the symptom burden.

Although systematic reviews appear to show that toxicities do not generally affect quality of life, in clinical practice, I think they do. For instance, sometimes patients with microsatellite-stable mCRC who are heavily treated with chemotherapy and then switched to single-agent pembrolizumab (used off-label) feel better despite scans showing progressing disease. This is owing to improved side effects and not drug efficacy. I believe that treatment-related toxicities are a major concern. In these subgroups, the quality of treatment helps quality of life.

Tanios S. Bekaii-Saab, MD Many of the quality-of-life questionnaires are not very patient-friendly. How can we make this measurement more relevant as we move forward with drug development? What are some of the challenges as we evaluate target-specific studies, which are often limited to a single-arm design?

Zev A. Wainberg, MD As a community, we have to make these questionnaires simpler. EORTC quality-of-life questionnaires are very long and convoluted. They incorporate many important elements, but they lack the ability to home in on critical quality-of-life issues. For example, they evaluate many issues that are peripheral and difficult to answer. I see my patients struggling to complete these questionnaires; most of the time, they give up halfway through. The questionnaires should focus on the critical aspects of treatment. They should ask questions such as, "How do you feel now compared with last week?" and "Are you spending more time in bed?"

Kanwal Raghav, MD, MBBS One answer is to develop better tools, better questionnaires, and better measures.[1] There are 2 other helpful strategies. The study of trifluridine/tipiracil included time to deterioration of performance status as an endpoint.[2] This is a good endpoint, but the question is how to best measure it. There are remote monitoring tools for physical activity measures that can be used. Physical activity is a strong indicator of overall quality of life. In the GERCOR OPTIMOX1 trial, mobility and pain were the quality measures that most reflected survival outcomes in colorectal cancer.[3] The group at my institution is currently evaluating the use of Fitbits to measure digital step counts in patients who are being treated with a salvage line of treatment. There are technological solutions that could provide a way to assess quality of life and allow researchers to intervene early when indicated.

These types of measurements could be incorporated into clinical trials, even single-arm studies. Quality-of-life measures from single-arm studies, whether single center or multicenter, would at least provide a body of literature with which to compare baseline, health-related quality-of-life indices.

Zev A. Wainberg, MD Investigators at my institution are performing similar studies with Apple watches. It will be hard to evaluate the data without a control arm, but we are trying to incorporate those measures, as Dr Raghav suggested.

Tanios S. Bekaii-Saab, MD The treatments for these patients are becoming increasingly refined. So, certainly this has become one of the building blocks for clinical trials and ultimately regulatory approval, not just in the United States, but in Europe and other places as well.

Kanwal Raghav, MD, MBBS There are initiatives from the National Cancer Institute moving toward patient-reported outcomes, like PRO Common Terminology Criteria for Adverse Events (CTCAEs), that will allow us to design trials that incorporate more patient-focused and symptom-focused tools. Of course, these PRO CTCAEs will not take into consideration financial toxicities or social issues that can also affect quality of life in these patients, but at least they can be used as very quick measures of drug-related toxicity and integrated with more comprehensive social and financial tools, in order to help accurately assess our patients and optimize their care in a holistic manner.

Disclosures

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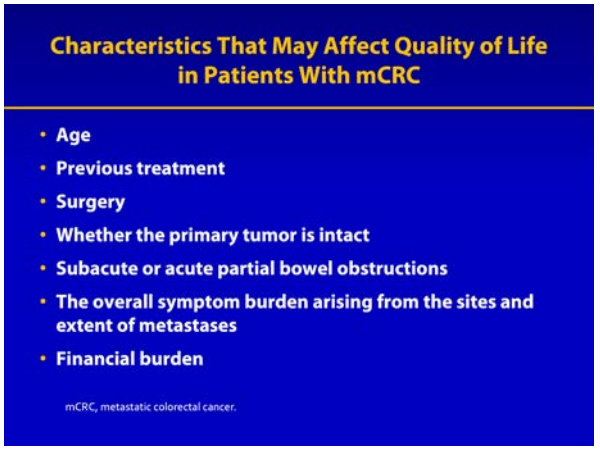

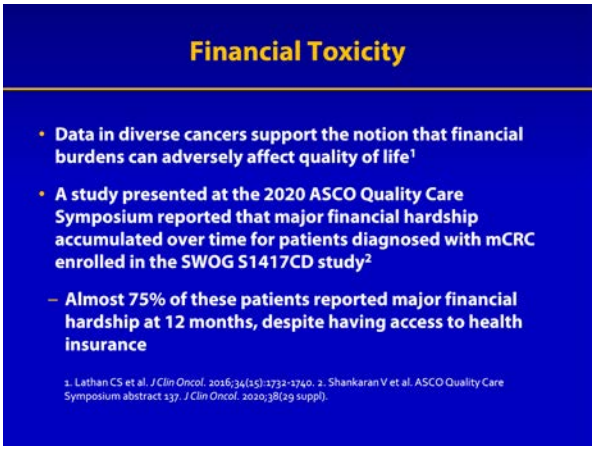

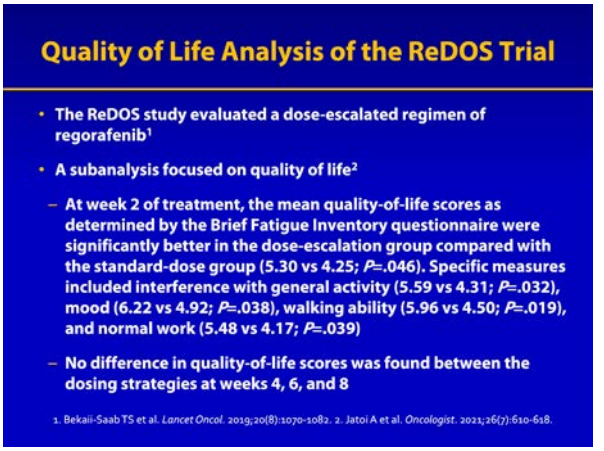

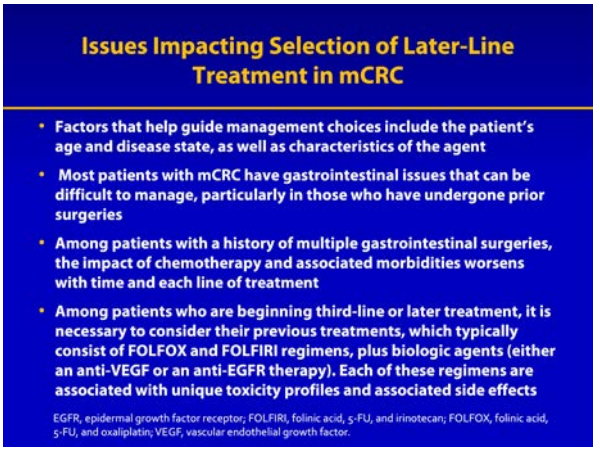

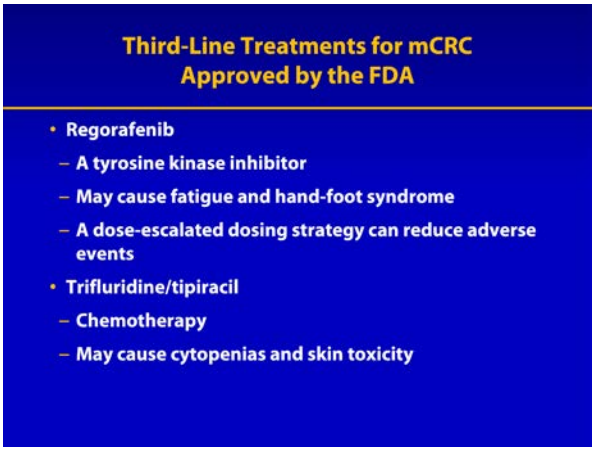

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