Current Colorectal Cancer Reports (2019) 15:105–111
https://doi.org/10.1007/s11888-019-00436-0

SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

Current Trends in Systemic Therapies in Elderly Patients With Metastatic Colorectal Cancer

Anna Griffith[1] · Hanna Sanoff[1]

Published online: 9 July 2019

Abstract

Purpose of Review The incidence of colorectal cancer increases with age and the population is aging, making treatment of elderly patients with metastatic colorectal cancer (mCRC) an increasingly common part of oncology practice. We review the literature regarding systemic treatment of colorectal cancer in the elderly population.

Recent Findings Most of the data for toxicity and efficacy of systemic therapies for mCRC in older patients comes from subgroup analysis of pooled phase II and III trials of both chemotherapy and targeted agents. These studies suggest that combination chemotherapy and targeted therapy are well-tolerated in fit elderly patients with slightly increased risk of toxicity.

Summary Assessment of functional status independent of age can help differentiate which patients are candidates for combination chemotherapy, single-agent chemotherapy, targeted therapy, or supportive care. Fit, elderly patients should be treated as younger patients. Dose-reduced doublet therapy with dose escalation as tolerated is a safe and effective way to treat less-fit elderly patients. Most targeted therapies appear to be safe in the elderly population without significant concerns for increased toxicity.

Keywords Metastatic colorectal cancer · Elderly · Targeted therapy · Systemic therapy · Comprehensive geriatric assessment

Introduction

Colorectal cancer is a leading cause of cancer death in the USA and developed countries. The incidence increases with age and 70% of new diagnoses are in patients over the age of 65 [1]. Most patients with mCRC are treated with a palliative intent and treatment typically involves systemic chemotherapy. Generally speaking, the treatment principles used to treat younger patients with mCRC can be applied to elderly patients, although with several important caveats.

Chronological age is a poor marker of functional status and the ability to tolerate treatment for advanced colorectal cancer. Decisions of whether and how to treat elderly patients should be based on functional status, medical comorbidities, and life expectancy, not age. In order to make a distinction between fit and frail elderly patients, traditional functional scoring systems are often used to predict a patient's ability to tolerate chemotherapy, including ECOG Performance Status, Karnofsky Performance Status (KPS), and Palliative Performance Scale (PPS). In general, patients with a poor performance status on any of these scales do not tolerate chemotherapy well and most agree that patients with a significant functional impairment, defined by ECOG PS of 3 or 4, should not be treated with systemic chemotherapy, but rather supported with palliative care. Conversely, fit elderly patients should be treated as younger patients with mCRC. The most difficult decision-making for providers is for elderly patients who are neither fit nor frail.

In making this distinction, it is important to realize that performance status estimated by ECOG and KPS tend to underrepresent the degree of functional impairment in an older patient [2]. Hurria et al. developed a predictive model to help providers predict toxicity in older cancer patients that incorporates both geriatric and traditional oncologic correlates of vulnerability. This involved a prospective multi-center trial of patients' age greater than or equal to 65 from seven institutions with various tumor types (27% GI) that studied the risk

This article is part of the Topical Collection on *Systemic Therapies in Colorectal Cancer*

✉ Anna Griffith
anna.griffith@unchealth.unc.edu

[1] UNC Hospitals, Hematology/Oncology, Physicians Office Building, 170 Manning Drive, 3rd Floor, Chapel Hill, NC 27599, USA

of grades 3–5 toxicity from chemotherapy. This data was used to develop a predictive model which included components of the geriatric assessment; laboratory test variables; and patient, tumor, and treatment characteristics to predict risk of grades 3–5 toxicity in patients. Low-risk patients (0–5 points) had a 30% risk of toxicity, intermediate patients (6–9 points) had a 52% risk of toxicity, and high-risk (10–19 points) had an 83% risk of toxicity [2].

Beyond the Hurria risk score, additional assessment using Comprehensive Geriatric Assessment (CGA) can further refine the clinical assessment of functional capacity to aid decision-making. CGA is a tool used by geriatricians to help identify frail older patients, and is recommended by ASCO in all patients aged 65 years and older [3••]. A complete assessment of this type includes a mini-mental status exam (MMSE) and assessment of activities of daily living (ADL) and instrumental activities of daily living (IADL). It is far more likely to expose important functional impairment in the elderly such as falls, social isolation, polypharmacy, and cognition. One prospective trial of different chemotherapy strategies in patients over the age of 75 suggests that impaired condition based on the MMSE and impaired autonomy, measured by impaired IADL, can be used to identify older patients at increased risk of severe treatment-related toxicity [4].

Not only is it important to address the unique functional challenges faced by older patients, clinicians much also consider how values might change with age. For example, available data suggests that older patients are just as willing to be treated with chemotherapy as younger patients; however, they are less tolerant of side effects of the therapy [4–6]. Because combination chemotherapy regimens, although more effective at controlling cancer, often cause more side effects than single-agent regimens, the potential benefit of longer survival must then be weighed against the increased likelihood of side effects. Unfortunately, there are few studies that adequately address how chemotherapy affects quality of life in older patients to inform decision-making.

Chemotherapy: Efficacy and Toxicity

The backbone of therapy for patients with mCRC not amenable to surgical resection remains combination chemotherapy with FOLFOX or FOLFIRI. As historically there have been a small number of elderly patients enrolled in clinical trials, it is challenging to know whether older patients glean the same benefit from treatment as younger patients, and challenging to provide patients with realistic expectations of their risk of chemotherapy toxicity. Several key subgroup analyses and pooled analyses from large phase II and III clinical trials guide provide us with safety and efficacy data in this population. The first of these is a retrospective analysis of 3825 patients who received 5-fluorouracil monotherapy regimens in 22 European trials, of which 629 patients were aged 70 years or older. When compared with patients less than 70 years of age, survival was equal and response rates did not differ between age groups [7]. The authors were not able to pool toxicity data for this analysis. However, toxicity was assessed in the initial adjuvant pooled analysis of 7 phase III randomized trials involving 3351 patients with stages II and III colon cancer treated with adjuvant fluorouracil and leucovorin or fluorouracil and levasimole. This study found equivalent efficacy in the older population, as well as no increase in the incidence of toxicity in the elderly age group except for leukopenia in one of the seven studies [8]. Together, these pooled analyses provide ample evidence that older patients with colorectal cancer seem to benefit from 5-FU.

Similar pooled analyses guide our use of combination chemotherapy in the elderly mCRC population. The largest of these to evaluate oxaliplatin-fluoropyrimidine combinations included over 3700 patients (614 over 70 years old) from four clinical trials [9]. Compared with younger patients, the 70 and older group was slightly more likely to experience grade 3+ neutropenia (49% versus 43%, $p = 0.04$) and thrombocytopenia (5% versus 2%, $p = 0.04$), but there was no increase in nausea/vomiting, diarrhea, overall severe adverse events, or 60-day mortality. Further, there was no suggestion that the additive effect of combination oxaliplatin-fluoropyrimidine over fluoropyrimidine monotherapy was modified by age, confirming similar efficacy in the elderly. These data on oxaliplatin combinations were subsequently confirmed by subgroup analyses within single trials [10, 11].

Irinotecan-fluorouracil combinations were evaluated in a pooled analysis of four phase III trials that enrolled 2691 patients (599 aged 70 years or older) [12]. Again, the combination regimens added similar incremental efficacy benefit compared with monotherapy in the older subgroup as in the younger, confirming that age does not modify the effect of combination chemotherapy. There was little difference in toxicity between age groups. These results were confirmed in the subgroup analysis of the BICC trial, which evaluated differing irinotecan and fluoropyrimidine combination regimens [13].

Together, these pooled and subgroup analyses of clinical trials of first-line chemotherapy for advanced, unresectable metastatic colorectal cancer provide ample evidence that chemotherapy is effective in fit elderly patients and that the toxicity patterns in fit elderly patients are comparable with those seen in younger populations. Further, evidence supports both oxaliplatin and 5-FU (i.e., FOLFOX) and irinotecan and 5-FU (i.e., FOLFIRI) as safe and effective in the older population. Thus, just as in younger patients, the decision about what chemotherapy to use should be tailored to patient preference regarding toxicity. Notably, the relative importance of adverse effects may change when considering treatment decisions in older patients. Sensory neuropathy is the dose-limiting toxicity of oxaliplatin, which results in damage to sensory fibers, including those responsible for proprioception. In patients

with pre-existing issues with gait or balance or baseline weakness, oxaliplatin-induced neurotoxicity has the potential to exacerbate pre-existing physical functional limitations and precipitate falls [14, 15••]. So while it is commonplace to select FOLFIRI rather than FOLFOX for patients with pre-existing neuropathy, such a decision may also be prudent for older patients with other limitations in their physical function, a history of falls, or gait instability. Other differences in toxicity are more subtle between regimens [16] and should be incorporated into a discussion about treatment selection with all patients.

MRC-FOCUS2 Trial

While the results from pooled patient data from clinical trials suggests little distinction needs to be made between treatment decisions in older and younger colorectal cancer patients, clinical trial eligibility necessarily restricts enrollment to the fittest patients, limiting the generalizability of these results to fit older patients. Clinical decision-making for the majority of older patients whose physical health and function falls between the categories of robust and frail is best informed by the MRC FOCUS2 trial. FOCUS2 was designed to address the optimal chemotherapy strategy—single agent versus doublet—for elderly patients with mCRC. FOCUS2 enrolled 459 elderly patients at 61 UK centers with previously untreated mCRC who were considered unfit for full-dose chemotherapy based on age, fragility, or both. The study utilized a 2 × 2 factorial randomization to assign patients to one of four groups, (A) infusional fluorouracil (B) oxaliplatin and fluorouracil, (C) capecitabine, or (D) oxaliplatin and capecitabine. All patients were started at 80% of standard dose and escalated at 6 weeks at the discretion of the treating physician. The dual primary endpoints of the trial were progression-free survival in the oxaliplatin vs no oxaliplatin comparison arms, and global quality of life in the 5-FU and capecitabine comparison arms.

Neither primary endpoint was met in the trial: the addition of oxaliplatin to 5-FU or capecitabine did not significantly improve progression-free survival (HR 0.84, 95% CI 0.69–1.01), and there was no significant difference in global quality of life between capecitabine and 5-FU-treated patients. Despite a lack of PFS benefit, patients treated with the oxaliplatin combinations had a higher response rate than those treated with single-agent 5-FU or capecitabine (38% vs 11%) and a higher rate of disease control (71% vs 46%) suggesting better overall treatment utility with the addition of oxaliplatin. Further, the oxaliplatin combination arms (with protocol-specified a priori 20% dose reduction) did not have a significantly higher rate of toxicity than the fluoropyrimidine monotherapy arms. However, capecitabine was associated with increased rates of toxicity than fluorouracil, and the highest rates of severe toxicity were seen in the CapeOx arm.

FOCUS2 offers considerable insight into optimal treatment regimen for older patients, demonstrating good tolerance of dose-reduced regimens, good disease control, and little detrimental quality-of-life effect from the additional of oxaliplatin. It also confirms that while it offers greater convenience, capecitabine is not better tolerated than 5-FU, and the greater convenience does not improve quality of life [4].

Targeted Therapies: Efficacy and Toxicity

In 2004, both bevacizumab and cetuximab were approved for metastatic colorectal cancer. Since then, additional vascular endothelial growth factor pathway agents, ramucirumab and aflibercept, and epidermal growth factor receptor inhibitor panitumumab, and the multi-targeted kinase inhibitor regorafenib have been added to the armamentarium of available agents. Most recently, immune checkpoint inhibitors nivolumab with or without ipilimumab, and pembrolizumab have been approved for the subgroup of microsatellite unstable colorectal cancers. The quality of evidence surrounding the benefit and safety of each of these drugs in older populations is variable.

Bevacizumab Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF). For patients with metastatic colorectal cancer, when used in combination with regimens containing fluoropyrimidine, irinotecan, or oxaliplatin, bevacizumab results in improved response rates, progression-free survival and overall survival [17]. VEGF inhibition is associated with cardiovascular side effects such as hypertension and arterial thromboembolic events, as well as wound healing complications and bleeding.

Arterial thromboembolic events (ATE) were recognized as a key safety concern shortly after bevacizumab's approval. Based on a pooled analysis of five pivotal bevacizumab trials in patients with metastatic solid tumors, prior ATE and age over 65 years were identified as the key risk factors for a treatment-related ATE event [18]. As such, this is the primary concern in regarding bevacizumab—and other VEGF active agents—in older patients. There are four main studies guiding our recommendations regarding use of bevacizumab in this patient population, summarized in Table 1.

The first is an analysis of 2526 patients over the age of 65 with metastatic colorectal cancer derived from the linked Surveillance, Epidemiology, and End Results (SEER)/Medicare database. This analysis showed a modest improvement in survival for patients treated with bevacizumab, but the addition of bevacizumab increased the risk of stroke (4.9 vs 2.5%). The risk of venous thromboembolism was not increased [19]. A later analysis of a larger dataset from the SEER database found a lower 3-year incidence of arterial thromboembolic disease with an excess risk of ATE of 3.5 additional cases per 1000 person years [20]. Other studies

Table 1 Summary table of bevacizumab trials

Trial	Brief description	Risk of arterial toxicity	Risk of venous toxicity
Effectiveness of bevacizumab with first line combination chemo for Medicare patients with stage IV colorectal cancer [16]	2525 patients > aged 65 years with mCRC	Stroke increased from 2.5 to 4.9%	Not increased
Bevacizumab use and risk of cardiovascular adverse events among elderly patients with colorectal cancer receiving chemotherapy: a population-based study [17]	6803 CRC patients aged > 65	3.5 additional cases of ATE per 1000 person years	Not reported
PRODIGE 20 study [18]	Randomized phase II trial of 102 patients aged > 75 with mCRC	Grades 3–4 hypertension increased from 6 to 14%	VTE increased from 6.1 to 9.8%
AVEX trial [19]	Randomized phase III trial of 280 patients aged > 70 with untreated mCRC	All grade hypertension increased from 5 to 19%	VTE increased from 4 to 8%

are consistent, suggesting an increased rate of arterial toxicity in elderly patients treated with bevacizumab. Two elderly specific prospective trials have been conducted. The PRODIGE 20 trial, a randomized phase II study of patients aged 75 years or older with mCRC showed an expected higher rate of grade 3–4 hypertension (14 vs 6%) in patients treated with bevacizumab and chemotherapy vs those treated with chemotherapy alone; however, other toxicities were not significantly higher with bevacizumab [21]. The AVEX trial is a multicenter trial of 280 patients aged 70 years or older with untreated mCRC. Patients were randomized to receive capecitabine with or without bevacizumab. The bevacizumab arm had a high rate of treatment discontinuation (25 vs 15%) and higher rates of all grade hemorrhage (27 vs 7%), HTN (19 vs 5%), and VTE (12 vs 5%) [22].

The use of bevacizumab clearly prolongs progression-free and overall survival in metastatic colorectal cancer, though the absolute benefit is modest. In light of the potential risk of ATE, patients need to be counseled on this balance, particularly older patients with a prior stroke or heart attack, or poorly controlled hypertension.

Ramucirumab and Aflibercept Ramucirumab is a monoclonal antibody that binds VEGFR-2 to prevent binding of all VEGF ligands, resulting in inhibition of angiogenesis. The use of ramucirumab is approved based on the RAISE phase III clinical trial which showed that addition of ramucirumab to FOLFIRI improved overall survival when compared with placebo and FOLFIRI in patients with previously treated mCRC [10]. In a subgroup analysis of the RASIE trial, the beneficial effect of ramucirumab was also noted in patients aging 65 years or greater and aging 75 years or greater. Importantly, the incidence of adverse reactions attributed to ramucirumab was not elevated in either of these groups.

Aflibercept, a VEGF-A, VEGF-B, and placental growth factor inhibitor, is another angiogenesis inhibitor approved for use in combination with FOLFIRI for the treatment of metastatic colorectal cancer. In the subgroup analysis of patients over the age of 65 treated in the pivotal VELOUR study, aflibercept's efficacy was not diminished in this older subgroup [23]. While there are not elderly-specific toxicity data available, given the mechanism of action and known adverse effects, the same cautions are warranted when considering the use of aflibercept in older patients with a history of arteriovascular disease.

Cetuximab and Panitumumab

Cetuximab and panitumumab are monoclonal antibodies that target the epithelial growth factor receptor (EGFR). Both agents are used in RAS wildtype advanced colorectal cancer either in combination with chemotherapy as first- or second-line therapy, or as single agents in patients with refractory disease. Few clinical trials have directly addressed the safety and efficacy of these drugs in the elderly population; however in general, these trials have no raised any major safety concerns.

For cetuximab, a retrospective series of 56 patients aged 70 years or greater with heavily pretreated KRAS WT colorectal cancer found no unexpected adverse events in those treated with cetuximab. As expected, there was a high rate of rash (75% of patients) and diarrhea (80%) [24]. An observational database in Germany studied 657 patients with mCRC receiving cetuximab therapy, 305 of whom were 65 years or older. There was a trend toward higher grade and longer duration of dermatologic and non-dermatologic toxicities in the older patients, but no major differences in tolerability by age [25]. A phase II trial of cetuximab and capecitabine that included 66 elderly patients with previously untreated mCRC noted a higher than expected incidence of acneiform rash with 30% of patients experiencing a grade 3 or 4 rash [26]. These studies suggest that patients over age 65 might be more susceptible to more severe or longer duration of toxicity, particularly rash.

In the subgroup analysis of the phase III trial comparing panitumumab to supportive care, the subgroup of patients over the age of 65 experienced similar efficacy of

panitumumab as patients younger than 65 [27]. Toxicity data were not presented by age strata. A retrospective analysis of 40 frail elderly patients who received panitumumab for mCRC in the first- or second-line setting revealed that roughly 25% of patients required dose reductions for toxicity, but no patients required treatment discontinuation [28]. Panitumumab monotherapy may be reasonable in patients with a ECOG PS of 3. This recommendation is based on a phase II trial of 33 patients with untreated mCRC and ECOG PS of 3 or less. These patients had a PFS of 7.9 months and there were no deaths or grade 4 toxicities related to panitumumab [29].

While there is less robust data on the safety and effectiveness of EGFR inhibitors in older patients, this available data does not show any major safety concerns. Elderly patients with mCRC, RAS WT tumors should be considered for EFGR inhibitors as clinically indicated, with careful attention to proactive rash management [30].

Regorafenib Regorafenib is an oral inhibitor of multiple kinases (e.g., VEGFR 1-3, TIE2) whose broad activity results in inhibition of cancer growth and proliferation, and angiogenesis. Reforganib's adverse effects include hypertension, hemorrhage, bowel perforation, fatigue, diarrhea, hand-foot skin reaction, and hepatotoxicity. Regorafenib was approached as a single agent for patients with chemotherapy refractory mCRC on the basis of the CORRECT trial [31••]. CORRECT compared best supportive care plus regorafenib or placebo in 760 patients and showed a significant survival benefit of 6.4 vs 5 months in regorafenib treated patients. The pre-planned subgroup analysis of elderly patients enrolled in the CORRECT trial showed similar efficacy in patients aged 65 years and older, but no report of toxicity in this population is available.

A small prospective phase II study evaluated alternative regorafenib dosing and schedule in 23 patients aged 75 years and older (32). Regorafenib was administered on a 2-weeks-on and 1-week-off schedule, beginning at a standard 160 mg/day in patients < 80 without comorbidity, 120 mg/day in patients considered vulnerable or with more than 1 comorbidity, and at 80 mg/day in patients 80 years and older or with a ECOG PS of 2. Using this alternative dosing, regorafenib was well tolerated with only 9% of patients discontinuing for adverse effects, and 9% grade 3 hand-foot syndrome and 9% grade 3 fatigue. Overall survival in this small cohort was promising at 8.9 months.

Conclusions

Treatment of colorectal cancer in the elderly is an increasingly important topic as the population ages. Treatment decisions should be based on geriatric-relevant clinical factors of functional status, medical comorbidities, and age-related organ function decline in conjunction with the values of each older individual with advanced colorectal cancer. A comprehensive geriatric assessment is useful in helping to define which elderly patients are most likely to tolerate chemotherapy and targeted therapies. There is nuance in choosing a therapy regimen for the subgroup of older patients who are neither fit nor frail, with little solid data to guide decision-making. The following general principles from recent literature are useful to guide these choices.

- Fit elderly patients should be treated in the same manner as younger patients, with standard doublet chemotherapy in the first-line setting. Careful attention to oxaliplatin neurotoxicity is warranted given concerns for altered proprioception and fall risk.
- Combination chemotherapy should be given at reduced doses or avoided in frail older patients.
- Capecitabine appears to be more toxic than fluorouracil in older patients, outweighing the potential benefit of greater convenience.
- Most targeted therapies have not been studied directly in the elderly population, but are likely well tolerated in patients fit enough to receive an intensive regimen.
- Bevacizumab (and ramucirumab and aflibercept) should be used with caution in older patients, and avoided in those with a history of stroke, MI, or uncontrolled hypertension.
- Cetuximab and panitumumab may have a higher incidence of skin rash in the elderly.
- Regorafenib may be used as monotherapy in the elderly, although dose reduction may be required to ensure tolerance.

Compliance With Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Ries L, Melbert D, Krapcho M, et al. SEER cancer statistics review, 1975-2015. Bethesda: National Cancer Institute. http://seer.cancer.gov/csr/1975_2015/ (Accessed on February 21, 2019)

2. Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol. 2011;29:3457–65. https://doi.org/10.1200/JCO.2011.34.7625.
3.•• Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients received chemotherapy: ASCO guidelines for geriatric oncology. J Clin Oncol. 2018;36:2326–47. https://doi.org/10.1200/JCO.2018.78.8687 **Guidelines for utilizing the geriatric assessment to identify vulnerabilities not typically captured with traditional oncology assessments.**
4. Aparicio T, Jouve JL, Teillet L, Gargot D, Subtil F, le Brun-Ly V, et al. Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients. J Clin Oncol. 2013;31:1464–70. https://doi.org/10.1200/JCO.2012.42.9894.
5. Sanoff HK, Goldberg RM, Pignone MP. A systematic review of the use of quality of life measure in colorectal cancer research with attention to outcomes in elderly patients. Clin Colorectal Cancer. 2007;6:700–9. https://doi.org/10.3816/CCC.2007.n.039.
6. Seymour MT, Thompson LC, Wasan HS, Middleton G, Brewster AE, Shepherd SF, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open label, randomized factorial trial. Lancet. 2011;377:1749–59. https://doi.org/10.1016/S0140-6736(11)60399-1.
7. Folprecht G, Cunningham D, Ross P, Glimelius B, di Costanzo F, Wils J, et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials. Ann Oncol. 2004;15:1330–8. https://doi.org/10.1093/annonc.mdh344.
8. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med. 2001;345:1091–7. https://doi.org/10.1056/NEJMoa010957.
9. Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. J Clin Oncol. 2006;24:4085–91. https://doi.org/10.1200/JCO.2006.06.9039.
10. Sastre J, Aranda E, Massutí B, Tabernero J, Chaves M, Abad A, et al. Elderly patients with advanced colorectal cancer derive similar benefit without excessive toxicity after first-line chemotherapy with oxaliplatin-based combinations: comparative outcomes from the 03-TTD-01 phase III study. Crit Rev Oncol Hematol. 2009;70:134–44. https://doi.org/10.1016/j.critrevonc.2008.11.002.
11. Arkenau HT, Graeven U, Kubicka S, Grothey A, Englisch-Fritz C, Kretzschmar A, et al. Oxaliplatin in combination with 5-fluorouracil/leucovorin or capecitabine in elderly patients with metastatic colorectal cancer. Clin Colorectal Cancer. 2008;7:60–4. https://doi.org/10.3816/CCC.2008.n.009.
12. Folprecht, et al. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. J Clin Oncol. 2008;26:1443–51. https://doi.org/10.1200/JCO.2007.14.0509.
13. Jackson NA, Barrueco J, Soufi-Mahjoubi R, Marshall J, Mitchell E, Zhang X, et al. Comparing safety and efficacy of first-line irinotecan/fluoropyrimidine combinations in elderly versus nonelderly patients with metastatic colorectal cancer: findings from the bolus, infusional, or capecitabine with camptostar-celecoxib study. Cancer. 2009;115:2617–29. https://doi.org/10.1002/cncr.24305.
14. Bullinger KL, Nardelli P, Wang Q, Rich MM. Oxaliplatin neurotoxicity of sensory transduction in rate proprioceptors. J Neurophysiol. 2011;106:704–9. https://doi.org/10.1152/jn.00083.2011.
15.•• Kerckhove N, Collin A, Conde A, Chaleteix C, Pezet D, Balayssac D. Long-term effects, pathophysiological mechanisms, and risk factors or chemotherapy-induced peripheral neuropathies: a comprehensive literature review. Front Pharmacol. 2017;8:86. https://doi.org/10.3389/fphar.2017.00086 **A comprehensive overview of the long-term effects of CIPN in cancer patients.**
16. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22:229–37.
17. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013–9. https://doi.org/10.1200/JCO.2007.
18. Scappaticci, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst. 2007;15:1232–9. https://doi.org/10.1093/jnci/djm086.
19. Meyerhardt JA, Li L, Sanoff HK, Carpenter W IV, Schrag D. Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. J Clin Oncol. 2012;30:608–15. https://doi.org/10.1200/JCO.2011.38.9650.
20. Tsai HT, Marshall JL, Weiss SR, Huang CY, Warren JL, Freedman AN, et al. Bevacizumab use and risk of cardiovascular adverse events among elderly patients with colorectal cancer receiving chemotherapy: a population-based study. Ann Oncol. 2013;24:1574–9. https://doi.org/10.1093/annonc/mdt019.
21. Aparicio T, Bouché O, Taieb J, Maillard E, Kirscher S, Etienne PL, et al. Bevacizumab+chemotherapy versus chemotherapy alone in elderly patients with untreated metastatic colorectal cancer: a randomized phase II trial-PRODIGE 20 study results. Ann Oncol. 2018;29:133–8. https://doi.org/10.1093/annonc/mdx529.
22. Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol. 2013;14:1077–85. https://doi.org/10.1016/S1470-2045(13)70154-2.
23. Cutsem V, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;28:3499–506. https://doi.org/10.1200/JCO.2012.42.8201.
24. Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015;5:660–71. https://doi.org/10.1016/S1470-2045(15)70127-0.
25. Bouchahda M, Macarulla T, Spano JP, et al. Cetuximab efficacy and safety in a retrospective cohort of elderly patients with heavily pretreated metastatic colorectal cancer. Crit Rev Oncol Hematol. 2008;67:255–62. https://doi.org/10.1016/j.clcc.2014.05.003.
26. Jehn CF, Böning L, Kröning H, Possinger K, Lüftner D. Cetuximab-based therapy in elderly comorbid patients with metastatic colorectal cancer. Br J Cancer. 2012;106:274–8. https://doi.org/10.1038/bjc.2011.554.
27. Sastre J, Grávalos C, Rivera F, et al. First-line cetuximab plus capecitabine in elderly patients with advanced colorectal cancer: clinical outcome and subgroup analysis according to KRAS status from a Spanish TTD Group Study. Oncologist. 2012;17:339–45. https://doi.org/10.1634/theoncologist.2011-0406.

28. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25:1658–64. https://doi.org/10.1200/JCO.2006.08.1620.
29. Pietrantonio F, Cremolini C, Aprile G, Lonardi S, Orlandi A, Mennitto A, et al. Single-agent panitumumab in frail elderly patients with advanced RAS and BRAF wild-type colorectal cancer: challenging drug label to light up new hope. Oncologist. 2015;20:1261–5. https://doi.org/10.1634/theoncologist.2015-0171.
30. Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28:1351–7. https://doi.org/10.1200/JCO.2008.21.7828.
31.•• Petrioli R, et al. Capecitabine plus oxaliplatin and bevacizumab, followed by maintenance treatment with capecitabine and bevacizumab for patients aged > 75 years with metastatic colorectal cancer. Clin Colorectal Cancer. 2018;17:663–9. https://doi.org/10.1016/j.clcc.2018.07.002 **Study demonstrating both efficacy and safety of CAPOX-bevacizumab followed by maintenance Cap and Bev in patients aged > 75 years with metastatic colorectal cancer.**