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Chemotherapy for colorectal cancer in the elderly

Jung Han Kim

Jung Han Kim, Division of Hemato-Oncology, Department of Internal Medicine, Kangnam Sacred-Heart Hospital, Hallym University Medical Center, Hallym University College of Medicine, Seoul 150-950, South Korea

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Correspondence to: Jung Han Kim, MD, PhD, Division of Hemato-Oncology, Department of Internal Medicine, Kangnam Sacred-Heart Hospital, Hallym University Medical Center, Hallym University College of Medicine, Shingil-ro 1, Youngdungpo-Gu, Seoul 150-950, South Korea. harricil@hotmail.com

Telephone: +82-2-8345414

Fax: +82-2-8464669

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Abstract

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the elderly. However, elderly patients with CRC tend to be under-presented in clinical trials and undertreated in clinical practice. Advanced age alone should not be the only criteria to preclude effective therapy in elderly patients with CRC. The best guide about optimal cancer treatment can be provided by comprehensive geriatric assessment. Elderly patients with stage III colon cancer can enjoy the same benefit from adjuvant chemotherapy with

5-fluorouracil/leucovorin or capecitabine as younger patients, without a substantial increase in toxicity. With conflicting results of retrospective studies and a lack of data available from randomized studies, combined modality treatment should be used with great caution in elderly patients with locally advanced rectal cancer. Combination chemotherapy can be considered for older patients with metastatic CRC. For elderly patients who are frail or vulnerable, however, monotherapy or a stop-and-go strategy may be desirable. The use of targeted therapies in older patients with metastatic CRC appears to be promising in view of their better efficacy and toxicity. Treatment should be individualized based on the nature of the disease, the physiologic or functional status, and the patient's preference.

Key words: Adjuvant chemotherapy; Colorectal cancer; Elderly; Palliative chemotherapy; Review

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Core tip: Colorectal cancer (CRC) is one of the leading causes of cancer-related death in the elderly. However, elderly patients with CRC tend to be under-presented in clinical trials and undertreated in clinical practice. In older patients with CRC, advanced age alone should not be the only criteria to preclude adjuvant or palliative chemotherapy that is effective in younger patients. This review provides readers with a better understanding of the potential benefit of chemotherapy in older patients with CRC.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common

malignancies, accounting for approximately 1.36 million new cases worldwide every year. It is the third most common cancer behind lung and prostate cancer in men and the second most common after breast cancer in women^[1]. CRC is a disease of aging and largely affects the elderly population^[2]. As estimated by the Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/csr/1975_2011), approximately 70% of cases in total develop over the age of 65 years, and about 40% of patients are over 75 years. Despite a substantial survival improvement in patients with CRC, probably due to improved detection and treatment^[3], the overall survival rate of older patients still remains low^[4].

The poor outcomes in the elderly population can be attributed to a variety of factors, such as low economic status, limited access to healthcare systems, and comorbid conditions. Undertreatment may also be one of the major factors that lead to the lower survival rate in the elderly with CRC^[5-8]. Undertreatment includes less aggressive diagnostic evaluation, less aggressive surgery, and less intensive chemotherapy, such as *ad hoc* anticipatory dose reduction or schedule alterations of regimens with established efficacy. Elderly patients with CRC tend to more often be inadequately staged and receive fewer elective operations^[5]. They are also less likely to receive adjuvant or palliative chemotherapy and/or radiotherapy^[6-8]. In a retrospective European cohort study of 110 CRC patients over 75 years of age^[9], 96 were surgically treated, but only 6/23 with stage III disease received adjuvant chemotherapy and 4/14 with rectal cancer were treated with adjuvant radiotherapy. Out of 18 patients with stage IV disease, only 3 received palliative chemotherapy.

A recent study conducted in the Netherlands shows that the long-term prognosis of older patients (aged 60-89 years) with CRC who survived the first year approaches that of middle-aged patients^[10]. These results indicate that elderly patients with a good health status can benefit from intensive therapy, including surgery, adjuvant chemotherapy and/or radiotherapy, or palliative chemotherapy. While the care of frail patients should focus on palliation, chronologic age should not determine the candidacy for adjuvant or palliative chemotherapy in elderly patients with CRC.

The lack of clear guidelines to guide treatment decisions for elderly patients may be an important reason for their undertreatment. Older patients are generally excluded from clinical trials^[11-13]. In a systemic review of 109 phase III or IV randomized controlled trials published in 2007^[13], 22 (20.2%) trials used an upper age limit exclusion criterion, and only 42 (38.5%) trials performed age-specific subgroup analyses. Due to the frequent exclusion of older patients from clinical trials, the evidence-based data for optimal treatment are lacking in spite of higher burden of CRC and worse prognosis in this age group. Clinicians often rely on evidence from clinical trials of

the general population to make treatment decision for older patients. However, extrapolating results from middle-aged adults to older patients who suffer complex comorbidities or cognitive impairment can be hazardous.

The major challenge of treating older patients with CRC is to assess whether the expected benefits of treatment are superior to the risk of morbidity or mortality. This review aims to provide readers with a better understanding of the potential benefit of systemic chemotherapy in older patients with CRC.

COMPREHENSIVE GERIATRIC ASSESSMENT

Advanced age is associated with an increase in other age-related health problems as well as increased incidence of cancer. Treatment in older patients with cancer is inevitably influenced by other conditions such as comorbidities, disabilities, and functional or cognitive status, along with tumor stage. Therefore, proper selection of patients is the key to delivering cancer treatments that are both effective and safe.

Geriatric conditions should be identified by comprehensive geriatric assessment (CGA) to guide optimal treatment. CGA is a multidisciplinary, in-depth evaluation to assess risk of morbidity, mortality, and life expectancy in older persons^[14,15]. CGA provides the tools to predict the functional age of the elderly with cancer based on comorbidities, nutritional status, cognitive function, socioeconomic status, polypharmacy, and geriatric syndromes.

CGA is helpful for clinicians to develop coordinated plans for optimal treatment in the elderly with cancer. However, it can be time-consuming in clinical practice and may not be practical for all patients. Some investigators have developed a brief CGA that is specific for older cancer patients, Cancer-Specific Geriatric Assessment (CSGA)^[16]. It assesses older cancer patients using validated measures with seven domains including functional status, comorbidity, polypharmacy, cognitive function, psychologic status, social functioning and support, and nutritional status. Results from the CALGB 360401 study demonstrated the feasibility of implementing CSGA in cooperative group clinical cancer trials^[17]. A prospective multi-center trial with 500 older cancer patients showed that CSGA is useful for predicting chemotherapy-related toxicity in older adults with cancer^[18].

ADJUVANT THERAPY

Colon cancer

Adjuvant chemotherapy has a role in patients with stage III and probably high-risk stage II colon cancer^[19-21]. In clinical practice, older patients are less likely to receive postoperative chemotherapy than younger patients because of the concern for

toxicity^[8,22]. In a retrospective cohort study utilizing the SEER/Medicare-linked database, 6262 patients aged 65 years and older with resected stage III colon cancer were identified from 1991 to 1996^[8]. Only 55% of elderly patients received adjuvant chemotherapy within three months after curative surgery. The likelihood of receiving adjuvant treatment declined dramatically with increasing age: 78% of patients aged 65-69 years, 74% of those aged 70-74 years, 58% of those aged 75-79 years, 34% of those aged 80-84 years, and 11% of those aged 85-89 years. Similar results were noted in another study of 85934 patients with stage III disease between 1990 and 2002^[22].

During 1990-2004, postoperative chemotherapy with leucovorin (LV)-modulated 5-fluorouracil (5-FU/LV) was the standard of care for stage III colon cancer, based on a 26% relative reduction in mortality compared with surgery alone^[19]. 5-FU/LV adjuvant chemotherapy seems to be as beneficial in older patients as it is in younger patients in terms of progression-free survival (PFS), disease-free survival (DFS), and overall survival (OS)^[23,24]. In a population-based cohort study of 3357 patients over 67 years of age with stage III colon cancer, the survival benefit of adjuvant chemotherapy with 5-FU/LV did not diminish with chronologic age^[23]. However, adjuvant therapy may be more toxic for elderly patients. In a SEER/Medicare-derived cohort study^[21], hospitalization for various chemotherapy-related toxicities increased steadily with increasing age. In a pooled analysis of 3351 patients with resected colon cancer, however, the relative benefit on both OS and time to tumor recurrence from adjuvant chemotherapy was similar across all age groups, with no increased incidence of toxicities among patients 70 years or older, except for leucopenia in one study^[24]. The oral fluoropyrimidine capecitabine can be an effective alternative to 5-FU/LV in the adjuvant setting. In a randomized phase III study of capecitabine vs bolus 5-FU/LV (Mayo Clinic regimen), capecitabine showed an equivalent DFS to 5-FU/LV and was associated with significantly fewer adverse events^[25]. Therefore, the selected elderly patients with stage III colon cancer can obtain the same benefit from adjuvant chemotherapy with 5-FU/LV or capecitabine as their younger counterparts, without a significant increase in toxicity.

In 2004, the Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial demonstrated that the addition of oxaliplatin to 5-FU/LV improved both DFS and OS in patients with stage III colon cancer^[20]. In an adjuvant setting, however, the benefit of adding oxaliplatin to 5-FU/LV (FOLFOX) for elderly patients is controversial^[26,27]. In a recent retrospective analysis, oxaliplatin-containing regimens showed only a small incremental survival benefit over non-oxaliplatin regimens for patients 75 years or older with stage III colon cancer^[26]. A pooled analysis of data from

adjuvant trials containing oxaliplatin showed no significant benefit in terms of DFS or OS compared to 5-FU/LV in patients older than 70 years^[27]. Subgroup analyses of major adjuvant trials also showed no benefit of adding oxaliplatin for older patients. The subset analyses of the NSABP C-07 trial found that the addition of oxaliplatin to 5-FU/LV yielded no survival benefit in patients older than 70 years with stage II or III colon cancer, with a trend towards decreased survival (hazard ratio = 1.18, 95% confidence interval: 0.86-1.62)^[28]. In the subset analyses of the MOSAIC trial, patients aged 70-75 years with stage II or III colon cancer showed a lack of survival benefit from the addition of oxaliplatin^[29].

Overall, the benefit and toxicities of 5-FU/LV or capecitabine as adjuvant chemotherapy appear to be similar in older and younger patients. With no data from prospective randomized studies, however, adjuvant chemotherapy with oxaliplatin-containing regimens needs to be considered on an individual basis for elderly patients 70 years or older (Table 1).

Rectal cancer

Combined modality therapy of total mesorectal excision surgery, radiation, and chemotherapy is the standard of treatment for younger patients with locally advanced rectal cancer. Because of the concern that treatment-related complications may outweigh the benefits of combined treatment^[30,31], however, this approach is not frequently used in elderly patients with rectal cancer. In a population-based study of 1807 patients 65 years or older who underwent surgical resection for stage II or III rectal cancer between 1992 and 1996, only 37% received both adjuvant 5-FU and radiation therapy^[32].

A systematic overview of 8507 patients with rectal cancer from 22 randomized trials demonstrated that perioperative radiotherapy could reduce the risk of local recurrence and death from rectal cancer^[33]. The Stockholm II trial, a population-based prospective randomized study, also observed similar benefits from preoperative radiotherapy of rectal carcinoma^[34]. However, the risk of non-cancer-related death was higher in both trials, especially in older patients treated with radiation^[33,34]. Cardiovascular disease was the major cause of intercurrent death following radiation. In addition, radiation therapy tends to be more toxic in older patients^[35,36]. Elderly patients appear to be at increased risk for radiation enteritis, probably due to pre-existing conditions such as hypertension, diabetes, and vascular diseases.

To the best of our knowledge, there are no data available from randomized studies of perioperative chemoradiation in older patients with rectal cancer. Several retrospective studies have reported that preoperative (neoadjuvant) chemoradiation therapy with 5-FU or capecitabine also increases the feasibility of anal sphincter-preserving surgery with an

Table 1 Major studies regarding adjuvant chemotherapy in elderly patients with colon cancer

| Ref. | Type of study | No. of total patients | No. of older patients/age (yr) | Endpoint | Outcome [HR (95%CI)] |
|---|---|-----------------------|--------------------------------|--|---|
| Iwashyna <i>et al</i> ^[23] | Population-based cohort study (SEER-Medicare) | 3357 | 3357 (100%)/≥ 70 | 5-FU <i>vs</i> observation: OS | OS: 0.73 (0.65-0.82) |
| Sargent <i>et al</i> ^[24] | Pooled analysis of 7 randomized phase III trials | 3351 | 506 (15%)/≥ 70 | 5-FU/LV <i>vs</i> observation: (1) TTR (2) OS | (1) TTR: 0.68 (0.60-0.76; <i>P</i> < 0.01) (2) OS: 0.76 (0.68-0.85; <i>P</i> < 0.01) |
| Sanoff <i>et al</i> ^[26] | Retrospective, database analysis (SEER-Medicare, NSYSR, CanCONS, NCCN) | 5489 | 5489 (100%)/≥ 75 | OS in stage III: (1) CTx <i>vs</i> no CTx (2) Oxaliplatin-based <i>vs</i> non-oxaliplatin regimens | (1) 0.60 (0.53-0.68) (2) SEER-Medicare: 0.84 (0.69-1.04) NYSR: 0.82 (0.51-1.33) |
| McCleary <i>et al</i> ^[27] | ACCENT group analysis in stage II / III | 14528 | 2575 (22%)/≥ 70 | 5-FU/LV or oral 5-FU <i>vs</i> combination regimens: DFS, OS, TTR in (1) older and (2) younger patients | (1) DFS: 1.05 (0.94-1.19; <i>P</i> = 0.09) OS: 1.08 (0.95-1.23; <i>P</i> = 0.05) TTR: 1.06 (0.93-1.22; <i>P</i> = 0.36) (2) DFS: 0.89 (0.80-0.99; <i>P</i> < 0.01) TTR: 0.88 (0.79-0.98; <i>P</i> = 0.02) OS: 1.08 (0.95-1.23; <i>P</i> = 0.04) ¹ |
| Yothers <i>et al</i> ^[28] | Exploratory subset analysis of updated results of NSABP C-07 trial | 2409 | 396 (16%)/≥ 70 | 5-FU/LV <i>vs</i> oxaliplatin plus 5-FU/LV: (1) DFS (2) OS | (1) DFS: 1.03 (0.77-1.36; <i>P</i> = 0.87) (2) OS: 1.18 (0.86-1.62; <i>P</i> = 0.30) |
| Tournigand <i>et al</i> ^[29] | Subgroup analysis of MOSAIC trial for stage II disease and elderly patients | 2246 | 315 (14%)/70-75 | 5-FU/LV <i>vs</i> FOLFOX4: (1) DFS (2) OS | (1) DFS: 0.93 (0.64-1.35; <i>P</i> = 0.73) (2) OS: 1.10 (0.73-1.65; <i>P</i> = 0.66) |

¹The benefit of adding oxaliplatin was restricted to patients younger than 70 years for OS. CTx: Chemotherapy; DFS: Disease-free survival; 5-FU/LV: 5-Fluorouracil/leucovorin; OS: Overall survival; TTR: Time to recurrence.

excellent downstaging in patients 70 years or older with locally advanced rectal cancer^[37,38]. Concerning the tolerance of this combined approach, however, there are conflicting results^[39,40]. A retrospective study of 36 patients over 70 years of age with rectal cancer reported that "vulnerable" elderly patients could receive the same neoadjuvant 5-FU-based chemoradiotherapy and undergo surgery as well as "fit" elderly patients, with similar tolerability and response rate^[39]. In another series of patients 75 years or older with rectal cancer, the majority of elderly patients required early termination of treatment, treatment interruptions, or dose reductions^[40]. These data suggest that combined modality therapy should be performed with more caution in elderly patients with rectal cancer.

Older patients should not be excluded only based on chronologic age from the curative treatment modality of rectal cancer. With a lack of data available from randomized studies, however, multidisciplinary evaluation and individualized treatment are recommended for older patients with rectal cancer. Medically fit older patients should be considered for the combined modality treatment that is useful for younger patients.

PALLIATIVE CHEMOTHERAPY

During the last decade, the management of metastatic CRC has been rapidly evolving with the use of biologic-targeted agents and the development of surgical techniques. The current chemotherapy of metastatic CRC involves various active drugs such as 5-FU/LV,

capecitabine, irinotecan, oxaliplatin, cetuximab, bevacizumab, panitumumab, ziv-aflibercept, and regorafenib, either in combination or as single agents.

Cytotoxic chemotherapy

Cytotoxic chemotherapy still remains the mainstay of treatment for patients with metastatic CRC. For many years, 5-FU/LV was the only active treatment for advanced CRC. Multiple studies demonstrated that this combination was effective and well tolerated in the elderly population, with similar benefits compared with younger cohorts^[41-43]. In a pooled analysis with 629 patients older than 70 years from 22 clinical trials, 5-FU-based palliative chemotherapy showed an equal OS (10.8 mo *vs* 11.3 mo, *P* = 0.31) and PFS (5.5 mo *vs* 5.3 mo, *P* = 0.01) in older and younger patients^[43]. In addition, no significant differences in severe toxicities were observed between older and younger patients^[41-43].

Capecitabine, an oral 5-FU, can be an alternative option for elderly patients with advanced CRC who are considered ineligible for combination chemotherapy. In a phase II trial of 51 patients older than 70 years with advanced CRC, capecitabine was effective and well tolerated: overall response rate (ORR) was 24%, with 7 mo of PFS and 11 mo of OS, and grade 3/4 adverse events were observed in 12%^[44].

Irinotecan, a topoisomerase I inhibitor, is also an active drug in metastatic CRC. For patients with metastatic CRC, irinotecan may be given as a single agent weekly or every three weeks. In a Phase III comparison of two irinotecan-dosing regimens

as second-line therapy of metastatic CRC, more than one third of 291 patients were older than 70 years^[45]. Chronologic age did not affect OS or PFS, but patients 70 years or older were at increased risk of grade 3/4 neutropenia and diarrhea compared with younger patients, suggesting that irinotecan should be administered with greater caution to elderly patients. A variety of combinations of irinotecan with 5-FU/LV or capecitabine are currently used in patients with metastatic CRC^[46-48]. In a combined analysis of 2691 patients from randomized controlled trials, the ORR and PFS were improved with irinotecan-based combination therapy compared with 5-FU/LV in both younger and older patients (older than 70 years)^[49]. In terms of toxicity, there were no significant differences between younger and older patients. In the BICC-C trial comparing safety and efficacy of first-line irinotecan/fluoropyrimidine (bolus, infusional, or capecitabine) combinations in elderly (older than 70 years) vs younger patients with metastatic CRC, these combination regimens were well tolerated in the elderly population, with similar efficacy to that found in younger patients^[50].

Oxaliplatin-containing regimens, such as FOLFOX, capecitabine plus oxaliplatin (XELOX), or irinotecan plus oxaliplatin, are also effectively used in patients with metastatic CRC. An open-label randomized factorial trial (MRC FOCUS2) investigated reduced-dose chemotherapy options in older and frail patients with metastatic CRC who would otherwise have been excluded from clinical trials^[51]. The study included 43% patients above 75 years and 13% older than 80 years, and patients were randomized in four arms (infusional 5-FU/LV, FOLFOX, XELOX, or capecitabine monotherapy). The addition of reduced-dose oxaliplatin to 5-FU/LV was not associated with a significant improvement of PFS (5.8 mo vs 4.5 mo, $P = 0.07$). Although the risk of grade 3/4 toxicities was not significantly increased with oxaliplatin, the replacement of 5-FU/LV with capecitabine resulted in a higher rate of severe toxicities with no improvement of quality of life. To minimize toxicities in older patients with metastatic CRC, stop-and-go strategies or maintenance 5-FU/LV-based chemotherapy may be a desirable option. The OPTIMOX1 study showed that FOLFOX-based chemotherapy stop-and-go strategy (6 cycles of FOLFOX7, 5-FU/LV maintenance without oxaliplatin for 12 cycles, and reintroduction of FOLFOX7) had similar efficacy and tolerability compared with FOLFOX4 until progression for patients aged between 76 and 80 years^[52].

Overall, most trials uniformly revealed that palliative cytotoxic chemotherapy in elderly patients with metastatic CRC showed similar efficacy and toxicity to what was observed in younger patients (Table 2). Combination chemotherapy should be considered for older patients with good performance status. For elderly patients who are frail or vulnerable, however,

monotherapy (5-FU/LV, capecitabine, or irinotecan) or stop-and-go strategy may be desirable to minimize toxicities.

Target therapy

The development of targeted therapies has substantially improved outcomes in various malignancies. Vascular endothelial growth factor inhibitor (bevacizumab)^[53-55] and anti-epidermal growth factor receptor antibodies (cetuximab and panitumumab) have been evaluated for older patients with metastatic CRC. In a pooled analysis of four randomized studies, the addition of bevacizumab to conventional chemotherapy significantly improved PFS and OS in patients older than 65 years with metastatic CRC^[53]. However, increases in arterial thromboembolic events (ATEs) were observed in patients 65 years or older in the bevacizumab group. In the BRiTE observational cohort study which assessed the safety and effectiveness of bevacizumab-based first-line therapy for metastatic CRC among a large cohort of elderly patients (896/1953 patients ≥ 65 years), the median PFS was similar across age cohorts (< 65 years, 9.8 mo; 65-75 years, 9.6 mo; 75-80 years, 10.0 mo; ≥ 80 years, 8.6 mo), but median OS decreased with age (< 65 years, 26.0 mo; 65-75 years, 21.1 mo; 75-80 years, 20.3 mo; ≥ 80 years, 16.2 mo)^[54]. There was no increased toxicity among elderly patients, except for the risk of ATEs. Recently, the AVEX trial, a multicenter phase III trial, investigated the efficacy and safety of adding bevacizumab to capecitabine in an older population^[55]. Patients older than 70 years with previously untreated metastatic CRC were recruited. Interestingly, all 280 patients were not deemed to be candidates for oxaliplatin- or irinotecan-based chemotherapy regimens. Although median OS did not differ significantly between the two groups, the addition of bevacizumab to capecitabine significantly improved ORR (19% vs 10%; $P = 0.04$) and PFS (9.1 mo vs 5.1 mo; $P < 0.01$). As expected, adverse effects, such as hemorrhage, hypertension, thromboembolic events, and proteinuria, were higher in the combination group. However, grade 3/4 toxicities were similar in the two groups, except for hand-foot syndrome and ATEs. These results suggest that the combination of bevacizumab and capecitabine is an effective and well-tolerated regimen for elderly patients with metastatic CRC.

Although cetuximab or panitumumab is less studied as first-line treatments in older patients with metastatic CRC, they can be an alternative choice for older patients with wild-type *KRAS* mutation. Two retrospective studies showed that cetuximab as a single agent or in combination with irinotecan had a favorable toxicity profile in elderly patients (70 years or older) with heavily pretreated metastatic CRC, and the efficacy was similar to that observed in younger patients^[56,57]. In a phase II study of a Spanish digestive tumor therapy group, cetuximab

Table 2 Major studies regarding palliative therapy in elderly patients with advanced/metastatic colorectal cancer

| Ref. | Type of study | No. of total patients | No. of older patients/age (yr) | Endpoint | Outcome |
|--|--|-----------------------|--------------------------------|---|--|
| Folprecht <i>et al</i> ^[43] | Retrospective analysis of data from 22 European trials | 3825 | 629 (16%) / ≥ 70 | 5-FU-based CTx in older <i>vs</i> younger patients (1) ORR (2) PFS (3) OS | (1) ORR: 23.9% <i>vs</i> 21.1%; <i>P</i> = 0.14 (2) PFS: 5.5 mo <i>vs</i> 5.3 mo; <i>P</i> = 0.01 (3) OS: 10.8 mo <i>vs</i> 11.3 mo; <i>P</i> = 0.31 |
| Folprecht <i>et al</i> ^[49] | Pooled analysis of data from four randomized phase III trials | 2691 | 559 (22%) / ≥ 70 | Irinotecan/5-FU <i>vs</i> 5FU as first-line CTx in younger and older patients: (1) ORR (2) PFS (3) OS | Improved with irinotecan-based CTx: (1) ORR: younger, 46.6% <i>vs</i> 29.0%; <i>P</i> < 0.01 elderly, 50.5% <i>vs</i> 30.3%; <i>P</i> < 0.01 (2) PFS: younger, HR = 0.77 (95%CI: 0.70-0.85; <i>P</i> < 0.01) elderly, HR = 0.75 (95%CI: 0.61-0.90; <i>P</i> < 0.01) (3) OS: younger, HR = 0.83 (95%CI: 0.75-0.92; <i>P</i> < 0.01) elderly, HR = 0.87 (95%CI: 0.72-1.05; <i>P</i> = 0.15) |
| Jackson <i>et al</i> ^[50] (BICC-C trial) | Randomized phase III in a 3-by-2 design | 430 | 117 (21%) / > 70 | Irinotecan + fluoropyrimidine at period 1 and irinotecan + 5-FU/LV + bevacizumab at period 2 in the older <i>vs</i> younger (1) PFS (2) OS | Period 1: (1) PFS: 7.5 mo <i>vs</i> 6.6 mo, HR = 0.98 (95%CI: 0.74-1.29) (2) OS: 21.2 mo <i>vs</i> 19.0 mo Period 2: (1) PFS: 10.6 mo <i>vs</i> 7.6 mo; <i>P</i> = 0.14 (2) OS: 19.4 mo <i>vs</i> 25.1 mo |
| Seymour <i>et al</i> ^[51] (MRC FOCUS2) | Open-label, multi-center, randomized phase III | 438 | 199 (43%) / ≥ 75 | a. IV infusion 5-FU/LV b. Oxaliplatin + 5-FU c. Oxaliplatin + capecitabine d. Capecitabine (1) PFS (a <i>vs</i> b and c <i>vs</i> d) (2) QoL with capecitabine instead of 5-FU | (1) PFS (addition of oxaliplatin <i>vs</i> no addition): 5.8 mo <i>vs</i> 4.5 mo, HR = 0.84 (95%CI: 0.69-1.01; <i>P</i> = 0.07) (2) Capecitabine did not improve QoL |
| Figer <i>et al</i> ^[52] (OPTIMOX1 study) | Exploratory cohort | 620 | 37 (6%) / 76-80 | FOLFOX4 until PD or FOLFOX7 for 6 cycles, maintenance without oxaliplatin for 12 cycles, and reintroduction of FOLFOX7 (1) PFS and (2) OS in the older <i>vs</i> younger | (1) PFS: 9.0 mo <i>vs</i> 9.0 mo; <i>P</i> = 0.63 (2) OS: 20.7 mo <i>vs</i> 20.2 mo; <i>P</i> = 0.57 (3) AEs ≥ grade 3: neutropenia, 41% <i>vs</i> 24%; <i>P</i> = 0.03, neurotoxicity, 22% <i>vs</i> 11%; <i>P</i> = 0.06 |
| Cassidy <i>et al</i> ^[53] | Retrospective pooled analysis (AVF2107g, AVF219g, NO16966, E3200 trials) | 3007 | 1142 (38%) / ≥ 65 | 5-FU/LV-based CTx ± bevacizumab (1) PFS (2) OS | (1) ≥ 65 yr: 9.3 mo (+ bevacizumab) <i>vs</i> 6.9 mo, HR = 0.58 (95%CI: 0.49-0.68; <i>P</i> < 0.01) ≥ 70 yr: 9.2 mo (+ bevacizumab) <i>vs</i> 6.4 mo, HR = 0.54 (95%CI: 0.44-0.66; <i>P</i> < 0.01) (2) ≥ 65 yr: 17.9 mo (+ bevacizumab) <i>vs</i> 15 mo, HR = 0.85 (95%CI: 0.74-0.97; <i>P</i> = 0.02) ≥ 70 yr: 17.4 mo (+ bevacizumab) <i>vs</i> 14.1 mo, HR = 0.7 (95%CI: 0.66-0.93; <i>P</i> < 0.01) |
| Cunningham <i>et al</i> ^[55] (AVEX trial) | Open-label, multi-center, randomized phase III | 280 | 280 (100%) / ≥ 70 | (1) PFS a. Capecitabine (<i>n</i> = 140) b. Capecitabine + bevacizumab (<i>n</i> = 140) (2) Assessment of treatment-related AEs | (1) PFS: 9.1 mo (+ bevacizumab) <i>vs</i> 5.1 mo, HR = 0.53 (95%CI: 0.41-0.61; <i>P</i> < 0.01) (2) AEs ≥ grade 3: 40% (+ bevacizumab) <i>vs</i> 22% |
| Sastre <i>et al</i> ^[59] (Spanish TTD Group Study) | Phase II | 66 | 66 (100%) / ≥ 70 | Cetuximab + capecitabine as first-line therapy (1) ORR (2) PFS, OS (3) Safety | (1) ORR: 31.8% (48.3% in w-KRAS <i>vs</i> 20.7% in m-KRAS; <i>P</i> = 0.027) (2) PFS: 7.1 mo, OS: 16.1 mo (3) AEs ≥ grade 3: paronychia (29.6%), rash (29.6%) |

AEs: Adverse events; CTx: Chemotherapy; 5-FU: 5-Fluorouracil; IV: Intravenous; m-KRAS: Mutant-type *KRAS*; ORR: Overall response rate; OS: Overall survival; PD: Progression of disease; PFS: Progression-free survival; QoL: Quality of life; w-KRAS: Wild-type *KRAS*.

as a first-line single agent was safe, but moderately active, with an ORR of 14.6% in patients aged 70 or older^[58]. However, another study of this same group

showed cetuximab plus capecitabine (at a dose of 1000 mg/m² every 12 h) was a safe and efficient regimen with an ORR of 48.3% in elderly patients with

advanced wild-type *KRAS* CRC^[59]. In an open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic CRC, panitumumab significantly improved PFS with manageable toxicity regardless of age, with the PFS, OS, and ORR similar in older and younger patients^[60]. Available data indicate that the absence of *KRAS* mutations is associated with higher response rates and PFS in patients with metastatic CRC treated with cetuximab or panitumumab^[59,61]. Therefore, *KRAS* mutation tests should be performed for the appropriate selection of patients who would benefit from cetuximab or panitumumab.

The use of targeted therapies in older patients with metastatic CRC appears to be promising in view of their better efficacy and toxicity than conventional cytotoxic chemotherapeutic agents (Table 2). However, because targeted agents can be associated with some unique or severe toxicities, these drugs should be administered with more caution under constant and careful monitoring for early detection of toxicities.

CONCLUSION

Although CRC is one of the leading causes of cancer-related death in the elderly, older patients tend to be under-presented in clinical trials, understaged, and undertreated. Advanced age alone should not be the only criteria to preclude effective adjuvant or palliative therapy in elderly patients with CRC. The best guide regarding optimal cancer treatment can be provided by careful CGA of the patient. All patients should be managed in the context of a multidisciplinary approach, and treatment should be individualized based on the nature of the disease, the physiologic or functional status of each patient, and the patient's preferences.

Elderly patients with stage III colon cancer can enjoy the same benefit from adjuvant chemotherapy with 5-FU/LV or capecitabine as younger patients, without a significant increase in toxicities. With conflicting results of retrospective studies and a lack of data available from randomized studies, combined modality therapy should be used with more caution in elderly patients with locally advanced rectal cancer. Combination chemotherapy can be considered for older patients with metastatic CRC. For elderly patients who are frail or vulnerable, however, monotherapy or stop-and-go strategy may be desirable. The use of targeted therapies in older patients with metastatic CRC appears to be promising in view of their better efficacy and toxicity. Finally, prospective studies are needed to develop evidence-based guidelines for older patients with CRC.

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