IJBC 2022; 14 (4): 116-124

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

Review article

How should we treat older patients with Metastatic Colorectal Cancer; A Review

Alfredo Colombo [1*], Ivan Fazio [2], Antonella Mazzonello [2], Tommaso Sciacchitano [1], Concetta Maria Porretto [1]

[1]Oncology Unit C.D.C. Macchiarella – Palermo (IT) - Viale Regina Margherita , 25
[2]Radiotherapy Unit C.D.C. Macchiarella – Palermo (IT)- Viale Regina Margherita , 25

ARTICLE INFO

Article History:
Received: 10/11/2022
Accepted: 12/12/2022

Keywords:
Metastatic colorectal cancer
Anti-EGFR
Chemotherapy
Toxicities

*Corresponding authors:
Alfredo Colombo, MD, PhD
Oncology Unit C.D.C Macchiarella - Palermo-Italy - - viale Regina Margherita 25
Email: alfredocolo63@gmail.com

Abstract

Nearly 50 % of newly diagnosed colorectal cancer, affect people over 70 years of age. Inclusion of older patients in clinical trials has been extremely rare. As a result, there is debate on how to manage these patients because it is still unclear how to balance the therapeutic advantages and toxicities. For patients who do not have comorbid conditions, with performance status (P.S.) 0–1, treatment guidelines are comparable to those for younger ones. Chemotherapy is an option for older patients; however, a full geriatric evaluation is recommended. Bevacizumab, an anti-vascular epithelial growth factor (anti-VEGF), combined with chemotherapy has become a standard of care in older patients. Anti-epidermal growth factor receptor (anti-EGFR) treatment is proposed both as monotherapy in the third-line or with chemotherapy in first or second line. Clinical trials that compared chemotherapy alone versus doublet chemotherapy plus anti-EGFR in older patients found that age is not an absolute contraindication for using anti-EGFR in first or second line. In fit older patients, anti-EGFR monotherapy in the first second or third line has demonstrated feasibility and antitumor efficacy. The major side effect is cutaneous rash which is easily managed. However, treatment in older patients should be carried out and be based on co-morbidities.

Please cite this article as: Colombo A, Fazio I, Mazzonello A, Sciacchitano T, Maria Porretto C. How should we treat older patients with Metastatic Colorectal Cancer; A Review. Iranian Journal of Blood and Cancer. 2022; 14(4): 116-124.

1. Introduction

According to estimates, in 2018 there were more than 1.8 million new cases of colorectal cancer (CRC) in the world [1]. In recent decades, this disease has increased in Western countries, where it ranks as the third-most frequent cancer in both women and men. The prevalence of unhealthy eating habits, smoking, inactivity, obesity, and population ageing, that are seen as indicators of socioeconomic development, are all factors of increased incidence. In France, new occurrences of CRC have been reported in 45% and 16% of individuals, respectively, aged > 75 and > 85 years [2]. The 5-year survival rate for patients with 75 years is 49.3%, and the 5-year survival rate for patients aged 65 years is 60% [2,3].

Patients over 70 years are underrepresented in clinical trials, even though older patients have a higher prevalence of cancer. The lack of data in these patients, and particularly in frail ones, is influenced by inclusion/exclusion criteria (performance status, organ dysfunction, and comorbidities), physician-related barriers (treatment tolerance and drug metabolism), and patient-related barriers (lack of autonomy and

logistical difficulties) [4].

The International Society of Geriatric Oncology (SIOG) defines older patients as those who are > 70 years of age [5]. Biological age should be distinguished from chronological age, since elderly patients are a heterogeneous population. Fit patients have few comorbidities, positive psychosocial conditions, and intact functional skills. Patients who lack autonomy and have a high number of comorbid conditions are defined "frail patients" [6]. For fit patients, indications are similar to those for younger ones [7]; for frail patients, chemotherapy is an option, but a comprehensive geriatric assessment (CGA) conducted by a geriatrician with expertise in oncology is mandatory. In order to better target older adults over 70 years of age, these patients should be required to undergo an assessment using a quick tool called G-8, an 8-item screening tool that explores different domains (physical health, mental health, functional issues, social issues, and environmental issues). The cut-off score is 14. Patients with a score over 14 are considered fit, instead, if the score is inferior to 14, patients are considered vulnerable and they should undergo a CGA [8,9].

A therapeutic strategy can not be achieved with only a G8 score when choosing or changing treatment dosage, however it could be helpful in establishing the necessary care for older patients. In this review we will discuss how to manage older patients with metastatic CRC (mCRC), with a particular focus on anti-VEGF and anti-EGFR.

2. Study design

A detailed search has performed through PubMed, Science Direct, Google Scholar, Scopus, MEDLINE. Research papers were searched using keywords such as Anti-EGFR, Older patients, chemotherapy, toxicities mCRC etc. Scientific papers that matched the keywords have been reviewed and findings have been noted herein.

2. Treatment stretegies

3.1. Age-related treatments and toxicities

The treatment options available for fit older patients with mCRC, are the same as for younger patients and include fluoropyrimidines (FPs) as monotherapy (Fluorouracil and capecitabine) or in combination with other compounds (FPs plus irinotecan and FPs plus oxaliplatin), targeted therapies (antiangiogenic agents such as bevacizumab or aflibercept; anti-EGFR antibodies such as cetuximab and panitumumab, or antimetabolites as trifluridine-tipiracile (TAS 102).

Regarding cancer therapies, some age-related conditions must be considered. With aging, polymedication is common, the bone marrow reserve is reduced, and glomerular filtration declines by 0.75 mL per year after age 40, with an increase of interactions with cytochrome P450 enzymes. [10].

Patients > 70 years and older are more prone to experience digestive skin toxicities with anti-EGFR. In situations of severe (grade 3 or higher) reactions, a dosage adjustment or withdrawal must be considered. Extermann et al. created the Chemotherapy Risk Assessment Scale for High-Age Patients, (CRASH) score, a model for predicting the risk of chemotherapy toxicity. Furthermore the Mini Mental Status Examination (MMSE) and the Instrumental Activities of Daily Living (IADL) scale are both indicators of chemotherapy toxicity [11].

3.2. Bevacizumab as a Single Agent or with Doublet Chemotherapy

In older chemotherapy naïve patients with mCRC, the clinical benefit of first-line doublet chemotherapy (5-FU or capecitabine with oxaliplatin, irinotecan, or 5-FU plus bevacizumab) compared to monotherapy (5-FU or capecitabine) is not clear.

Showing a superior objective response rate (ORR) without significant toxicities, the FOCUS 2 study, randomized 459 older and frail patients with advanced mCRC (median age, 74 years). The conclusion was that a combination with oxaliplatin was preferred to single-agent FPs. The progression-free survival (PFS), primary end point and overall survival (OS) secondary endpoints were not reached [12].

In seventy-one older patients with mCRC (median age, 80 years), the FFCD 2001-02 phase III randomized trial, compared irinotecan with 5-FU doublet treatment with 5-FU monotherapy. The irinotecan arm had a higher tumour response rate compared to the monotherapy arm (46.4% vs. 27.4%; p =.002), although the PFS difference between experimental arm versus control arm was not statistically significant (7.3 vs. 5.2 months; p =.15). [13]. Aparicio et al. employed geriatric tools such as MMSE, IADL, and Geriatric Depression Scale (GDS) scores, in patients who were randomized in the mentioned study. They showed that geriatric parameters might predict severe toxicity (MMSE score < 27/30 (OR, 3.84) and impaired IADL score (OR, 4.67) as well as unexpected hospitalisation (MMSE score 27/30 (OR, 4.56) [14] and later showed a

trend in favour of the IADL being independently associated with improved OS [15].

Bevacizumab was found to be effective in two studies when added to treatment for elderly patients. The first, AVEX trial, randomized 280 patients over 70 years old, who were deemed ineligible for intensive chemotherapy. Capecitabine and bevacizumab were administered twice daily and compared versus capecitabine alone. The PFS significantly improved in the association arm (9.1 versus 5.1 months). These patients had minor comorbidities, mainly arterial hypertension, and were in good general condition (ECOG 0-1). The majority of grade 3–4 adverse events (2% and 2%, respectively) were thromboembolic events and arterial hypertension.

In the second trial, a phase II study, PRODIGE 20, bevacizumab and chemotherapy were combined in 75 year old patients [17]. A combined criteria of tumour control and quality of life was the primary end point. PFS was 7.8 months compared to 10.7 months for the bevacizumab arm. The predominant toxicity was hematological with grade 3-4. A second publication revealed that there was no quality-of-life impact and that the IADL score was a predictor of effectiveness and tolerance [18].

In 1225 older patients with mCRC, a meta-analysis evaluated the therapeutic benefit of first-line doublet chemotherapy (containing oxaliplatin or irinotecan) in comparison to single-drug treatment 5-FU [19]. A cut-off age of 70 years was determined for oxaliplatin and 75 years for irinotecan.

Doublet treatment versus 5-FU alone significantly increased PFS (HR 0.82, CI 0.72–0.93) but did not OS (HR 1.00, CI 0.89-1.13).

A recent meta-analysis with a cut-off age of 70 or 75 years includes 10 trials and 1652 older patients in first line with mCRC [20]. Overall survival (OS) and progression-free survival (PFS) were statistically improved with the addition of bevacizumab to FPs (HR 0.78, 95% CI 0.63-0.96 and HR 0.55, 95% CI 0.44-0.67, respectively).

Oxaliplatin did not statistically improve OS (HR 0.99,95 % CI 0.85–1.17) but improved PFS (HR 0.81, 95% CI 0.67–0.97), as did irinotecan (HR 1.01, 95% CI 0.84–1.22 and HR 0.82, 95% CI 0.68–1.00, respectively).

The authors concluded that adding bevacizumab to FPs seems to be more useful in terms of OS and PFS than adding oxaliplatin or irinotecan. Regardless of the additional drug, both oxaliplatin given to 5-FU first-line doublet chemotherapy (FOCUS 2), and irinotecan with 5-FU (as in the FFCD 2001-02 research), showed modest benefit but increased toxicities and a decline of quality of life (QoL).

3.3. Anti-EGFR treatments

When used alone or in combination with chemotherapy, the anti-EGFR monoclonal antibodies, cetuximab and panitumumab, enhance outcomes in older patient RAS wild-type mCRC [21–23].

3.3.1. Anti-EGFR and doublet Chemotherapy

3.3.1.1 First Line

Regarding the use of anti-EGFR antibodies, international guidelines recommend not to take the patient's age into account [5,7,24]. Data on anti-EGFR in elderly patients, are few. Clinical trial comparisons by age classes are only phase II trials, retrospective studies, cohort studies, and post hoc subgroup analysis. Some post hoc studies revealed good results using this combination regimen in fit older patients who underwent doublet chemotherapy with anti-EGFR in clinical trials.

In the CRYSTAL and OPUS studies, Cetuximab was evaluated as a first-line therapy in combination with FOLFIRI and FOLFOX.

In the CRYSTAL trial, patients were aged between 19 to 84, whereas in the OPUS study, they were between 30 and 82 years. Folprecht conducted a pooled analysis of these studies [25]. Eight hundred forty-five patients with KRAS wild type mCRC were included in the combined analysis of the two trials.

Patients aged over 70 years were assigned to chemotherapy alone in 67 cases and chemotherapy with cetuximab in 78 cases. Patients under 70 years and over 70 years had similar median OS (23.3 and 23.6 months, respectively; p=.38). The addition of cetuximab improved OS, PFS, and overall response rate (ORR) in both older and younger patients; nevertheless, the differences were not statistically significant in the older group (presumably as a result of the limited power; p =.78 for PFS and p =.23 for response rate). The safety profiles of the two groups were comparable. Patients under 70 years of age (at risk of dehydration) treated with chemotherapy plus cetuximab experienced a higher frequency of diarrhoea, however this difference in incidence did not reach statistical significance (23.1% vs. 14.9%).

FIRE3 study assessed FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line therapy in 592 patients KRAS wild-type mCRC, aged 27 to 79 years. In each arm, around 45% of the patients were older than 65 years.

Independent of age, there was a non-significant advantage in OS (secondary end points) for the combination of cetuximab plus chemotherapy compared to bevacizumab plus chemotherapy: HR 0.75 (95% CI 0.56-1.01) for the 318 patients under 65 years and HR 0.80 (95% CI 0.58-1.09) for the 274 patients over 65 years [26].

PRIME Study [23,27,28] evaluates in first line FOLFOX4 plus panitumumab versus FOLFOX4 alone in 1183 KRAS wild-type mCRC in patients under eighty five years of age (40% of patients were more than sixty five years old) [23,27]. A post hoc evaluation expanded RAS analyses beyond KRAS exon 2 and studied the impact of age [28]. For PFS, the HR was 0.66 (95% CI 0.52–0.83) in patients <65 years (n=316) and 0.88 (95% CI 0.65–1.19) in patients > 65 years (n = 89). For OS, the HR was 0.75 (95% CI 0.58–0.96) in patients < 65 years and 0.80 in patients > 65 years old. Nevertheless, patients > 75 years did not benefit from FOLFOX + panitumumab in overall survival. Grade 3–4 toxicities associated to panitumumab had been primarily cutaneous toxicities (37%), diarrhoea (18%) and hypomagnesemia (7%). The rate of serious adverse events was higher in patients > 65 years who received chemotherapy plus panitumumab compared to those who received chemotherapy alone (41% vs. 16%).

3.3.1.2. Second line

Studies in second line on older patients with mCRC, treated with anti-EGFR and chemotherapy, revealed modest increase in survival. Patients aged 65 years and older who received a cetuximab chemotherapy combination were compared in a German cohort [29]. A total of 657 patients were enrolled of whom 305 were above 65 years of age. Ninety-five % of patients had at least one palliative therapy, and 80% had a low ECOG score of 1-2. Regardless of the age group, the rates of PFS and ORR were not different.

The older patients had more grade 3–4 cutaneous toxicities, and this difference was statistically significant (p =.05). Peters et al. [30,31] conducted a study in second line KRAS wild-type mCRC with age-specific analysis; panitumumab was administered in addition to FOLFIRI. When chemotherapy was combined with panitumumab (n = 208 pts) compared to chemotherapy alone (n = 213 pts), the median PFS improved for both patients over 65 and under 65 (6.4 vs. 4.6 months, p =.0089 and 6.4 vs. 3.9 months, p =.077). Although statistical significance was not reached, older patients' median OS significantly improved: 15.7 vs. 15.0 months (p=.27) for patients over 65 and 18.7 vs. 12.2 months (p=.12) for patients under 65.

3.3.1.3. Conclusion

In comparison to chemotherapy alone, in the first-line or second line, the clinical trials using doublet chemotherapy with anti-EGFR (cetuximab or panitumumab) demonstrate that age is not an absolute contraindication for this regimen. The advantage is still not evident, because the age limit is also not established (under or over 65 years), and not accurately represent the older patient population.

The anti-EGFR safety profile was satisfying, although there were greater cutaneous and digestive side effects, which may be hard to treat in older patients.

3.3.2. Anti-EGFR used alone or in Combination with Single-Drug Chemotherapy

Some rare studies have evaluated the effectiveness of anti-EGFR with single-drug chemotherapy or as a single agent in chemotherapy-refractory patients not deemed to benefit from doublet chemotherapy. It is interesting to note that several of these trials focused on anti-EGFR monotherapy in frail patients.

3.3.2.1.First line

Sastre et al. [32] led one study in 66 older patients with performance status between 0 and 1. This trial evaluated the effectiveness of cetuximab with capecitabine as a first-line therapy in patients with median age of 77 years; (range, 70-87 years). Because only 58 out of 66 patients (88%) had KRAS status and the capecitabine dose was decreased for safety, the results were compromised. The ORR was 31.8%, however the KRAS wild-type tumour subgroup had a greater response rate (48.3%) than the cohort with KRAS mutations.

For the total population, the median PFS and OS were 7.1 months and 16.1 months, respectively. Overall response rates, PFS, and OS were low and comparable to those from traditional chemotherapy.

With a significant incidence of severe paronychia (29.6%), which decreased after adjusted capecitabine dosage (7.7%), the safety profile was poor. The three-arm MRC COIN study also revealed a potential antagonistic interaction between capecitabine and cetuximab [33].

PANEL GITuD-2011-01 [34], a phase II trial, enrolled 26 older patients (age 70 years) with RAS and BRAF wild-type mCRC. They received panitumumab with capecitabine until progression of disease or intolerable toxicity. The first analyses revealed a median PFS of 9.6 months and a median OS of 23.7 months, an overall objective response of 38% with 27 % of cutaneous toxicity (rash) of grade 3.

In SAKK 41/10 study [35], vulnerable older patients with mCRC were assessed to study the efficacy of cetuximab, either alone or in combination with capecitabine. Patients were RAS/BRAF-wild-type with age ranging from 71 to 89 years. The study was stopped due to slow accrual after the inclusion of 24 patients (11 in the monotherapy arm and 13 in the combination arm;). In the monotherapy and combination arms, the response rates were 9% and 38%, respectively, with the combination arm having a greater frequency of toxicities and more treatment discontinuation.

The phase II study FRAIL [36] enrolled frail older patients with mCRC, KRAS-wild type with panitumumab as a first-line monotherapy. Thirty three patients were enrolled; their ages ranged from 73 to 89 years (median 81 years); 57.6% had an ECOG performance status of 2 and 69.7% of patients had three or more comorbidities. There were 18 patients (54.5%) with stable disease, and the objective response rate was 9.1% (all partial responses). Median PFS and OS were, respectively, 4.3 (95% CI 2.8-6.4) and 7.1 (95% CI 5.0-12.3) months.

Clinical response and KRAS status were significantly correlated (p =.037). Thus, the median PFS was 7.9 months, and the median OS was 12.3 months in the extended wild-type RAS sample (wild-type exons 2, 3, and 4 of KRAS and NRAS, n=15). The 6-month PFS rate was 53.3% (95% CI 30.1-75.2). The most frequent grade 3-related adverse event was acneiform rash (15.2%), and no grade 4 or grade 5 adverse events were reported.

OGSG 1602 [37] is a phase II study that enrolled patients with unresectable mCRC RAS wild-type naïve for chemotherapy and deemed inappropriate for intensive treatment.

Thirty-four patients (with a median age of 81 years) received panitumumab 6 mg/kg every two weeks.

The ORR was 50.0%, and the stable disease rate was 26.5%. According to the study the authors concluded that panitumumab monotherapy demonstrated good effectiveness and feasibility in frail or older patients with unresectable mCRC.

3.3.2.2. Second line

Most of the studies using anti- EGFR in the second line are retrospective. The main prospective study evaluating anti-EGFR monotherapy (as a first- or second-line treatment) was conducted by Pietrantonio et al. with ORR as primary endpoint [38].

This study assessed the efficacy of panitumumab monotherapy in 40 older patients with mCRC, RAS e BRAF wild type (median age, 80 years; range, 76-90). Although 82% of the patients had an ECOG performance status of 0-1, they were deemed frail. In patients who had contraindications to chemotherapy, panitumumab was used as a first-line treatment in 25% of cases, and as a second line in 75% of cases (previous treatments included oxaliplatin-based doublet chemotherapy in 43% of cases, capecitabine monotherapy in 37% of cases, and capecitabine plus bevacizumab in 20% of cases). The disease control rate was of 72.5% (no complete response), while the ORR was 32.5%.

The median PFS and OS were 6.4 and 14.3 months, respectively. Skin rash was the most common grade 3 adverse event (20%), but there were no permanent treatment discontinuations.

3.3.2.3. Third line

Jonker et al [39] enrolled 572 patients with previously treated colorectal cancer, with immunohistochemically detectable EGFR. Patients received Cetuximab plus BSC (287 patients) or BSC alone (285 patients). Cetuximab significantly increased both overall survival (primary end point) (6.1 months versus 4.6 months, HR 0.77; 95% CI, 0.64 to 0.92; P=.005) and PFS (HR 0.68; 95% CI, 0.57 to 0.80; p <.001). In the cetuximab arm, partial responses were obtained in 23 patients (8.0%).

Skin rash was the most common grade 3 adverse event (20%), however no permanent treatment discontinuations were noted.

Although the incidence of any adverse event of grade 3 or more was higher in the cetuximab group than in the BSC group (78.5% versus 59.1%, p <.001), quality

of life was better preserved in the cetuximab group than in the BSC alone group with less deterioration in physical function and global health status scores ($p < .05$). Van Cutsem et al. [40] enrolled 463 patients randomly allocated to the panitumumab or BSC groups. Although the study was not explicitly performed on older patients, 187 of the 463 patients were over 65 years old, with a median age of 62 years (range: 27–83). All except one of the patients had undergone at least two previous chemotherapy regimens.

Significantly longer PFS (8.0 vs 7.3 weeks; $p <.0001$) and ORR (10% vs 0%; $p <.0001$) were observed in the panitumumab arm compared to the BSC arm. OS (crossover was allowed) showed no difference. Diarrhoea, hypomagnesemia, and skin toxicity were the most frequent toxicities with panitumumab. No patients experienced infusion reactions of grade 3/4.

Panitumumab non-inferiority compared to cetuximab was evaluated in the ASPECCT trial [41]. In this multicentre randomized phase III head-to-head study, 999 evaluable patients (345 with an age> 65 years) with chemotherapy refractory metastatic colorectal cancer (mCRC), ECOG performance status of 0–2, and KRAS wild-type exon 2 were randomized to receive either panitumumab or cetuximab as monotherapy.

With a median OS of 10.4 months (95% CI, 9.4-11.6) for panitumumab and 10.0 months (9.3-11.0) for cetuximab (HR 0.97; 0.84–1.11), panitumumab noninferiority was shown.

Despite the lack of statistical significance, the HR for OS was 0.85 (0.67-1.08) in patients > 65 and 1.04 (0.87-1.23) in patients < 65 years of age and the same pattern in favour of panitumumab was seen for PFS (HR 0.86 IC 0.69-1.07); patients > 65 and (HR 1.10 IC 0.94–1.28) for patients < 65.

3.3.2.4 Conclusion

A phase III clinical trial to evaluate the effectiveness of anti-EGFR as a monotherapy or in combination with a single chemotherapy agent in older patients has not been carried yet. All trials utilising anti-EGFR as a single drug in frail patients have a small number of participant and are not comparative. When the anti EGFR single agent was compared with conventional chemotherapies, the objective response rate and survival rates were relatively similar, but we observed a higher toxicity profile. The safety of anti-EGFR monotherapy in this frail older group was tolerable, with mainly side effects on the skin, which were easily managed.

4. More recent studies

Anti-EGFR treatment in older patients with mCRC has been the subject of several clinical and observational investigations.

EREBUS is an observational study conducted in France, with the primary objective of determining the rate of metastatic resection in 389 patients with KRAS wild-type mCRC (aged 27 to 88 years) who had originally unresectable metastases and received cetuximab with chemotherapy as a first-line treatment [42].

One hundred and sixteen patients (72.4%) in the subgroup of older patients (> 70 years) had an ECOG performance status of 0 or 1. Irinotecan and oxaliplatin were used respectively in combination with anti-EGFR chemotherapy for 56.8% and 38.5% of patients. The results were comparable in older and younger patients. The median PFS was 9.5 months (95% CI 7.1-10.5) compared to 9.2 months (95% CI, 8.1-9.8), while the ORR was 46.5% (95% CI 37.4-55.6) compared to 56.7% (95% CI 50.8-62.6).

Jehn et al. enrolled 497 patients with metastatic colorectal cancer who received cetuximab and irinotecan and pre-treated with irinotecan [43]. Patients aged <65 or > 65 years had identical ORR, respectively 38.1% vs. 36.4% ($p =.57$). PFS was the same for all patients (6.0 months < 65 years and 6.2 months >65 years ($p = .99$).

ObservEr study evaluated retrospectively impact of age (< and >70 years) in patients who received chemotherapy and cetuximab for KRAS wild-type mCRC [44]. Regarding PFS and disease control rates, there were no age-related differences. Patients under 70 years had a greater median OS (27 months, 95% CI 22.7-31.3) than patients over 70 years old (19 months, 95% CI 14.7-23.4; $p =.002$).

This difference was probably caused by a higher percentage of liver resections and II-line chemotherapy in younger patients.

The PANDA trial, a non-comparative phase IIA study, valued in first-line, FOLFOX plus panitumumab vs. 5FU/leucovorin plus panitumumab in older patients (>70 years) with RAS and BRAF wild-type mCRC. [45]. Patients were stratified from baseline CRASH scores and geriatric evaluation using the G8 scale. PFS was the primary end point, while secondary end points include a prospective assessment of the G8 score prognostic value and correlation of CRASH risk categories with toxicity and OS.

At median follow up of 20,5 months, PFS in the experimental arm was 9.1 months (CI 95% 7.7-9.9) and in the control arm was 9.6 months (CI 95% 8,8-10.0) In older patients (>70 years) with RAS and BRAF wild-type mCRC, OPAL study, a phase II single arm trial, evaluated the effectiveness and safety of first-line treatment with panitumumab plus FOLFIRI [46]. Only patients who have one or fewer comorbidities and a performance status of 0 –1 will be included. Every eight weeks, the tumour response will be assessed until disease progresses.

MONARCC [47] is a prospective non-comparative randomized phase II trial conducted in untreated patients RAS and BRAF wild type mCRC were > 70 years of age or older. Patients were given panitumumab monotherapy or panitumumab with 5FU as first line. PFS at 6 months was the primary end point for a simple size of 80 patients.

5. Disussion

Older patients are underrepresented in clinical trials. The prevalence of patients over 75 years and beyond in mCRC makes this scenario more remarkable. Three-quarters of older CRC patients were found to be ineligible for clinical trials in the recent research by Canou-Poitrine et al. (1/3 of eligible patients were not invited to participate, and 17% of invited patients were not included) [48]. Patients over 80 also had a lower chance of being accepted for a study and receiving an invitation.

Many frail patients are not treated since there is little information regarding the correct management of this population given the absence of data for this group.

In Clinical practice management, decisions are based on data collected from younger patients with mCRC. Fit older patients should be treated with chemotherapy and targeted therapy, according to guidelines for the management of mCRC patients.

Guidelines suggest combining bevacizumab with chemotherapy because it has been shown to increase survival. Less intensive treatments are suitable in first or second-line for unfit older patients who are unable to receive conventional combination chemotherapy (with or without targeted drugs) [5,7]. Reduced-dose oxaliplatin with 5-FU or lower-dose capecitabine plus bevacizumab may be administered to these older patients [5].

Age is not a contraindication for standard regimens in fit older patients, as demonstrated by subgroup analyses of clinical trials with doublet chemotherapy with anti-EGFR, comparing chemotherapy alone with cetuximab (CRYSTAL, OPUS, and FIRE3 trials), panitumumab (PRIME study),or cetuximab (Jehn et al study), or panitumumab (Peeters et al. study), as second-line therapy.

In frail older patients, anti-EGFR (cetuximab in the Sastre et al study or panitumumab in the PANEL study) [32,34] combined with single-agent chemotherapy, failed to significantly improve survival and had more toxicities than chemotherapy alone.

The anti EGFR as single agent was well tolerated. Notably, there was a strong correlation between clinical response and RAS mutations in the FRAIL study (36) or Pietrantonio study [38] producing intriguing findings.

Clinical trials in older patients utilising anti-EGFR alone or in combination with a single monotherapy are limited, despite that this is still the standard for first or second line off-label treatments.

The incidence of cutaneous, digestive, and hypomagnesemia toxicities was higher in older patients using anti-EGFR, and these toxicities should be closely monitored.

An accessible method to evaluate toxicity and mortality prediction scores has just been published [49]. These results will eventually need to be verified in more metastatic and adjuvant colorectal investigations.

In conclusion, doublet chemotherapy plus anti EGFR or anti VEGF are the standard for fit patients under 75 years, while patients beyond 75 years should proceed with caution. International guideline stated that in frail patients, anti-EGFR monotherapy, whether used as an off-label first-line or second line, has no age restriction. Older patients should get treatment with caution, and the dose should be regulated in accordance with comorbidities.

Authors contributions

AC and CMP collaborated on the paper's conception and wrote the paper. CMP reviewed the paper and approved the final version of the article to be published.

Funding

No funding for this paper.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394–424.
2. Les cancers en France, Les Données, INCa. édition https://www.e-cancer.fr/content/download/255246/3573612/file/Cancers_en_FranceEssentiel_Faits_et_chiffres- 2018.pdf; 2018.
3. Holleczek B, Rossi S, Domenic A, et al. On-going improvement and persistent differences in the survival for patients with colon and rectumcancer across Europe 1999- 2007 - results from the EUROCARE-5 study. Eur J Cancer 2015; 51:2158–68.
4. Gouverneur A, Salvo F, Berdai D,Moore N, Fourrier-Reglat A, Noize P. Inclusion of elderly or frail patients in randomized controlled trials of targeted therapies for the treatment of metastatic colorectal cancer: a systematic review. J Geriatr Oncol 2018; 9:15–23.
5. Papamichael D, Audisio RA, Glimelius B, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol 2015; 26:463–76.
6. Jarrett PG, Rockwood K, Carver D, Stolee P, Cosway S. Illness presentation in elderly patients. Arch Intern Med 1995; 155:1060–4.
7. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:
1386–422.
8. Soubeyran P, Bellera C, Goyard J, et al. Validation of the G8 screening tool in geriatric oncology: the ONCODAGE project. J Clin Oncol 2011; 29:9001.
9. Soubeyran P, Bellera C, Goyard J, et al. Screening for vulnerability in older cancer patients the ONCODAGE prospective multicenter cohort study. PLoS One 2014;9:
e115060.
10. Shafiei M, Yoon R, McLachlan A, Boddy A, Beale P, Blinman P. Pharmacokinetics of anticancer drugs used in treatment of older adults with colorectal Cancer: a systematic review. Ther Drug Monit 2019; 41:553–60.
11. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. Cancer 2012; 118:3377–86.
12. Seymour MT, Thompson LC, Wasan HS, et al. Chemotherapy options in elderly and rail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomized factorial trial. Lancet 2011; 377:1749–59.
13. Aparicio T, Lavau-Denes S, Phelip JM, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02). Ann Oncol 2016; 27:121–7.
14. Aparicio T, Jouve JL, Teillet L, 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.
15. Aparicio T, Gargot D, Teillet L, et al. Geriatric factors analyses from FFCD 2001-02 phase III study of first-line chemotherapy for elderlymetastatic colorectal cancer patients. Eur J Cancer 2017; 74:98–108.
16. Cunningham D, Lang I, Marcuello E, et al. Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomized phase 3 trial. Lancet Oncol 2013;14: 1077–85.
17. Aparicio T, Bouche O, Taieb J, 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; 29:2270.
18. Aparicio T, Bouche O, Francois E, et al. Geriatric analysis from PRODIGE 20 randomized phase II trial evaluating bevacizumab + chemotherapy versus chemotherapy alone in older patients with untreated metastatic colorectal cancer. Eur J Cancer 2018; 97:16–24.
19. Landre T, Uzzan B, Nicolas P, et al. Doublet chemotherapy vs. single-agent therapy with 5FU in elderly patients with metastatic colorectal cancer. A meta-analysis. Int J Colorectal Dis 2015; 30:1305–10.
20. Landre T, Maillard E, Taleb C, et al. Impact of the addition of bevacizumab, oxaliplatin, or irinotecan to fluoropyrimidin in the first-line treatment of metastatic colorectal cancer in elderly patients. Int J Colorectal Dis 2018; 33:1125–30.
21. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis
of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol 2011; 29:2011–9.
22. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26:1626–34.
23. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol 2010; 28:4697–705.
24. VanderWalde N, Jagsi R, Dotan E, et al. NCCN guidelines insights: older adult oncology, version 2.2016. J Natl Compr Canc Netw 2016; 14:1357–70.
25. Folprecht G, Köhne C, Bokemeyer C, et al. Cetuximab and 1st-line chemotherapy in elderly and younger patients with metastatic colorectal cancer (MCRC): a pooled analysis of the CRYSTAL and OPUS studies. Ann Oncol 2010; 21:194.
26. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. Lancet Oncol 2014; 15:1065–75.
27. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 2014; 25:1346–55.
28. Douillard J, Siena S, Peeters M, Koukakis R, Terwey J, Tabernero J. Impact of baseline age on efficacy and safety of first-line panitumumab + FOLFOX4 vs FOLFOX4 treatment. Ann Oncol 2014;25 iv187.
29. Jehn CF, Boning L, Kroning H, Possinger K, Luftner D. Cetuximab-based therapy in elderly comorbid patients with metastatic colorectal cancer. Br J Cancer 2012;106:
274–8.

30. Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010; 28:4706–13.
31. PeetersM, Price T, Cervantes A, et al. Impact of baseline covariates and prior therapy on the efficacy of second-line panitumumab + FOLFIRI vs FOLFIRI treatment. Ann Oncol 2014;25 (iv187-iv8).
32. Sastre J, Gravalos 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.
33. Maughan TS, Adams RA, Smith CG, et al. Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomized phase 3 MRC COIN trial. Lancet 2011; 377:2103–14.
34. MéndezMéndez JC, Ramos M, De la Cámara Gómez JC, et al. First-line panitumumab plus capecitabine for the treatment of elderly patientswith wild-type KRASmetastatic colorectal cancer: preliminary results of the phase II, PANEL GITuD-2011-01 study. Ann Oncol 2017;28.
35. Kienle DL, Dietrich D, Ribi K, et al. Cetuximab monotherapy and cetuximab plus capecitabine as first-line treatment in older patients with RAS- and BRAF wild-type
metastatic colorectal cancer. Results of the multicenter phase II trial SAKK 41/10. J
Geriatr Oncol 2019; 10:304–10.
36. Sastre J, Massuti B, Pulido G, et al. First-line single-agent panitumumab in frail elderly patientswithwild-type KRAS metastatic colorectal cancer and poor prognostic factors: a phase II study of the Spanish cooperative group for the treatment of digestive tumours. Eur J Cancer 2015; 51:1371–80.
37. Ohta K, Kato T, Goto M, et al. Phase II study of panitumumab monotherapy in chemotherapy-naïve frail or elderly patients with unresectable, RAS wild-type colorectal cancer: OGSG 1602. ASCO Gastrointestinal Cancers Symposium 2020; 38:106 January 23-25.
38. Pietrantonio F, Cremolini C, Aprile G, 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.
39. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007; 357:2040–8.
40. 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.
41. Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomized, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol 2014; 15:569–79.
42. Rouyer M, Fourrier-Réglat A, Noize P, et al. Efficacité et sécurité d'emploi du cétuximab en traitement de 1re ligne du cancer colorectal métastatique chez les sujets âgés: résultats de la cohorte EREBUS. Rev Epidemiol Sante Publique 2016; 64 (S271-S2).
43. Jehn CF, Boning L, Kroning H, Pezzutto A, Luftner D. Influence of comorbidity, age and performance status on treatment efficacy and safety of cetuximab plus irinotecan in irinotecan-refractory elderly patientswithmetastatic colorectal cancer. Eur J Cancer 2014; 50:1269–75.
44. Rosati G, Pinto C, Di Fabio F, et al. Quality of life, compliance, safety and effectiveness in fit older metastatic colorectal patients with cancer treated in first-line with chemotherapy plus cetuximab: a restrospective analysis from the ObservEr study. J Geriatr Oncol 2018; 9:243–8.
45. Battaglin F, Schirripa M, Buggin F, et al. The PANDA study: a randomized phase II study of first-line FOLFOX plus panitumumab versus 5FU plus panitumumab in RAS and BRAF wild-type elderly metastatic colorectal cancer patients. BMC Cancer
2018;18:98.
46. Feliu J, Salud A, Losada EP, et al. First-line treatment with panitumumab plus FOLFIRI in elderly patients with RAS/BRAF wild-type unresectable metastatic colorectal cancer and good performance status: OPALO trial. J Clin Oncol 2018; 36:3618.
47. Tebbutt NC, Steer CB, Sjoquist KM, et al. MONARCC: a randomized phase II study of panitumumabmonotherapy and panitumumab plus 5 fluorouracil as first-line therapy for RAS and BRAF wild type metastatic colorectal cancer: an AGITG clinical trial. ASCO Gastrointestinal Cancers Symposium 2020;38: TPS271 January 23-25.
48. Canoui-Poitrine F, Lievre A, Dayde F, et al. Inclusion of older patients with Cancer in clinical trials: the SAGE prospective multicenter cohort survey. Oncologist 2019;24 (e1351-e9).
49. Retornaz F, Guillem O, Rousseau F, et al. Predicting chemotherapy toxicity and death in older adults with Colon Cancer: results of MOST study. Oncologist 2020;25(1): e85–93. https://doi.org/10.1634/theoncologist.2019-0241.