Role of chemotherapy and novel biological agents in the treatment of elderly patients with colorectal cancer

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Abstract

Patients older than 65 years are the fastest growing segment of the cancer population. It is estimated that within 20 years over 75% of cases and 85% of deaths from colorectal cancer (CRC) will be in this setting. Concerns about cancer treatment in the elderly relate to comorbidities, which increase proportionally with age, physiological changes associated with aging which may influence drug metabolism and toxicity, and diminishing life expectancy, which particularly impacts decisions surrounding the benefits of adjuvant therapies. Over the last 10 years, significant improvements in the treatment of advanced CRC with combination therapy have been made. The randomized trials which have defined these improvements did not exclude elderly patients. However, the median age of patients in these trials has generally been approximately 60 years. Thus, it appears that some degree of selection is involved with younger and presumably fitter patients being the subjects in most of the pivotal trials. The availability of new molecularly targeted agents and newly improved existing agents has expanded the range of treatment options available. This variety gives greater flexibility in dealing with different subsets of patients, such as the elderly. However, some fit elderly patients seem to tolerate combination therapy reasonably well, while studies on unfit elderly subjects are needed.

INTRODUCTION

Advancing age is often associated with an increase in cancer diagnosis. Malignancies represent the second cause of death in the elderly population in the Western countries, and this age group represents more than half of all diagnosed cancers. Due to a continuous increase in life expectancy, we may expect a higher rate of older patients with malignant disease in the future, and a growth in health expenses. However, to date few data are available in the literature about the treatment of this group of patients. Elderly patients have been under-represented in or excluded from clinical studies, mainly because older age is chosen to be an exclusion criterion. Very often, these patients are not treated because many believe the cancer growth potential to be lower in older subjects than in younger ones. Thus, many elderly cancer patients receive general supportive care. If this choice is a valid option for that group of patients defined as “frail”, this is not justifiable for all elderly patients. Often, oncologists fear heavy toxicities or suffer the patients and their relatives prejudice toward collateral effects resigning chemotherapy. However, in the Royal Marsden Hospital, no statistically significant difference in the overall or severe toxicity between the population aged 70 or older or the younger cohort was observed during adjuvant treatment for colorectal cancer (CRC) with a 5-fluorouracil (5-FU)-based chemotherapy. The only exception was stomatitis, which was more frequent in the older age group (19% vs 11%, P = 0.01). Regardless, when one plans a chemotherapy treatment in an older patient it is necessary to take into consideration the incidence and severity of myelosuppression, mucositis, nausea and vomiting, cardiomyopathy and peripheral neuropathy can increase above 70 years of age. On this basis, it is necessary to individualize a strategy to better tailor the treatment plan at the individual level. The assessment of the functional status by means of the widely used Karnofsky or Eastern Cooperative Oncology Group (ECOG)
does not seem as effective in older patients as in the adult population, because comorbidities in the elderly may interfere with the measurement of the performance status (PS)[3]. Several instruments have been proposed to monitor comorbidities, although none has been validated or widely accepted by the oncologic community[3]. A Comprehensive Geriatric Assessment (CGA) scale was thus developed and validated by the Italian Group for Geriatric Oncology (GIoGer) (Table 1)[3]. The functional, emotional and cognitive status, comorbidities number, and the numbers of those with depression and geriatric syndromes may help to better define populations that may or may not benefit from various therapeutic approaches (Table 2). Another problem is the definition of “elderly” patient. There is a widely variable perception of the age at which a patient is considered elderly, and this is based on chronological rather than physiological age. In studies of the treatment of acute myeloid leukaemia, patients over 60 were considered elderly while patients with solid tumors had to be over 70[3]. These differences make data comparison among clinical studies more difficult. Besides these factors, changes in the elderly also occur in terms of the functions of several organs. Noteworthy are alterations in kidney and liver functions as well as the apparent bone marrow reserve. In addition, elderly patients very often have additional medication, which may significantly influence the p450 cytochrome function. For this and other reasons clinicians are unwilling to treat an elderly patient. This paper will review the current therapeutic armamentarium suitable for CRC patients and its applicability to elderly subjects both in the adjuvant setting and in advanced disease.

### ADJUVANT CHEMOTHERAPY

Patients with newly diagnosed CRC have a median age of 70 years. Local recurrence or distant metastases are frequent within the first two years. The mean life expectancy of a 65-year-old man is approximately 13 years and for a 65-year-old woman the mean life expectancy is estimated to be nearly 19 years. Thus, an effective reduction in the occurrence of a disease relapse due to an adjuvant chemotherapy may be of major importance for these patients, as their life expectancy exceeds the time in which the appearance of metastatic disease would compromise their survival. On the other hand, a pooled analysis of individual patient data from seven phase III randomised trials (involving 3351 patients) in which the effects of postoperative 5-FU plus leucovorin (LV) or levamisole were compared with the effects of surgery alone in patients with stage II or III colon cancer has demonstrated a benefit in terms of overall survival (OS) in each age group[3]. The patients were grouped into four age categories of equal size, and analyses were repeated with 10-year age ranges (≤ 50, 51 to 60, 61 to 70, and > 70 years). OS and the time to tumor recurrence were significantly longer in patients treated with 5-FU-based therapy than in patients who did not receive adjuvant treatment (P < 0.001). No significant interaction was observed between age and treatment effect for OS or freedom from tumor recurrence, regardless of how age was included in the analysis. The survival curves for the patients who were older than 70 years of age converged slightly after five years, probably because of deaths from other causes. Analyzing the toxicities according to age for the two treatment regimens, the authors found age was not significantly related to the rate of grade 3 or higher nausea or vomiting, stomatitis or diarrhea among patients treated with either 5-FU plus LV or 5-FU plus levamisole. Although increased age was associated with higher rates of severe leukopenia in patients treated with 5-FU plus levamisole (P ≤ 0.001), this relationship was of borderline significance in patients who received 5-FU plus LV (P = 0.05). However, this analysis denotes some critical aspects.

| Group | Description | Treatment |
|-------|-------------|-----------|
| 1     | Healthy, good PS | Standard cancer treatment |
| 2     | Partially dependent, ≤ 2 comorbidities | Standard cancer treatment |
| 3     | Frail patients who are totally dependent with ≥ 3 comorbidities or 1 geriatric syndrome | Palliation |

The principal limitation of this study concerns its potential applicability to the general population of elderly patients. As a result of exclusion criteria and screening, elderly patients who enter clinical trials are a select group, with good PS, easy access to transportation and limited numbers of comorbidities. How co-existing conditions, malnutrition and poor social support might affect the efficacy and tolerability of 5-FU-based chemotherapy is unknown. It will be up to further studies to explain the decision to treat an elderly patient who has several other problems involving physician, patient and family. Moreover, only 23 of the 3351 patients (0.7%) in the trials were over the age of 80 years. Caution is therefore advised in extrapolating these findings to octogenarians.

Capecitabine is being investigated for the treatment of elderly patients with CRC. The X-ACT trial, comparing
oral capecitabine monotherapy (1250 mg/m² twice daily for 2 wk on/1 wk off) with the Mayo Clinic regimen (bolus 5-FU 425 mg/m² days with LV 20 mg/m² days 1-5 every 4 wk) in the adjuvant setting among 1987 patients with Dukes’ C colon cancer, reported significantly superior relapse-free survival with capecitabine (P = 0.041), and fewer adverse events than with 5-FU plus LV (P = 0.001)⁹. As a result, capecitabine monotherapy is now approved for adjuvant therapy of Dukes’ C colon cancer. Diaz-Rubio et al provided a retrospective safety analysis on a subpopulation of patients ≥ 70 years of age (capecitabine: n = 186; 5-FU/LV: n = 205) from the X-ACT trial database⁹. With respect to all-grade non-hematologic adverse events, elderly patients treated with single-agent capecitabine had significantly less diarrhea (52% vs 68%, P = 0.002), stomatitis (23% vs 67%, P < 0.001), and nausea (33% vs 47%, P = 0.005) than patients treated with bolus 5-FU/LV. Only all-grades hand-foot syndrome (HFS) was seen significantly more frequently with capecitabine (63% vs 8%, P < 0.0001). With respect to grade 3 or 4 hematologic adverse events, elderly patients had significantly less neutropenia with capecitabine than 5-FU/LV (4% vs 31%, P < 0.00001). Grade 3 or 4 hyperbilirubinemia was significantly greater with capecitabine than 5-FU/LV, when measured by NCI Common Terminology Criteria for Adverse Events. Although these results are promising, additional efficacy, quality of life (QoL), and cost data, particularly from the X-ACT trial, are needed to assess the usefulness of capecitabine for the treatment of elderly patients with CRC in the adjuvant setting.

A recent retrospective, age-based (< or ≥ 70 years), pooled analysis including 3742 CRC patients (614 age ≥ 70) was conducted extrapolating data in the Sanofi-Aventis database from four clinical trials testing the combination of oxaliplatin plus 5-FU/LV administered bimonthly (FOLFOX4) in the adjuvant, first-, and second-line settings⁸. End points included grade ≥ 3 adverse events, response rate (RR) (in advanced disease), progression or relapse-free survival, dose-intensity, and OS in the studies with mature survival data. The advantages of FOLFOX4 have been demonstrated in stage III patients¹⁰. The four trials formed the basis for the US Food and Drug Administration approval of FOLFOX4 in the treatment of metastatic CRC (first- and second-line settings) in stage III patients (after complete surgical resection). There was no difference in efficacy derived between younger and older patients enrolled into these trials with respect to RR, relapse/progression-free survival or OS. The analysis showed similar toxicity patterns in the two age groups. Increased rates of neutropenia (43% vs 49%; P = 0.04) and thrombocytopenia (2% vs 5%; P = 0.04) were observed in the older patients. However, efficacy outcomes were not different between the two age groups. In addition, drug delivery doses did not differ significantly by patient age and there was no difference in the incidence of treatment-associated deaths or neuropathy as a consequence of age. However, older patients who enrolled in these trials clearly are a select group, suggesting that generalizations derived from this study must be applied cautiously to individual older patients.

**CHEMOTHERAPY FOR ADVANCED DISEASE**

**5-FU**

Treatment of patients with metastatic disease is palliative. As for any other age group of patients, concern may be raised whether an elderly patient might benefit most from general supportive care rather than from toxic treatments. If one considers that patients with a new diagnosis of CRC have a median age of 70 years, the first endpoint remains symptoms palliation or clinical benefit, and not the objective response (OR) or OS time. Renal elimination of 5-FU after its catabolism in the liver and mucosa is limited and estimated to account for no more than 10% of excreted drug¹³. Therefore, 5-FU dose reduction in patients with renal dysfunction (possible in the older population) is usually not considered necessary. On the other hand, a large amount of 5-FU has to be metabolized by extrhepatic tissue. On this basis, a mild decrease in renal or hepatic function related to age is not a sufficient reason to reduce a 5-FU dose. A study examined the potential influence of gender and age on 5-FU-clearance⁸. Both factors are considered to have potential roles in the pharmacokinetic variability of drugs. There was no evidence that age modified 5-FU-clearance when it was adjusted for sex and dose. Female sex turned out to be a major determinant for increased toxicity, while age was not. These data quite justify the use of this drug in elderly patients. A large number of clinical trials confirm these assumptions. An Italian Group treated patients with a median age of 75 (range 70 to 85 years) with best supportive care or a weekly 5-FU bolus and LV regimen¹⁰. Interestingly, the median survival of the patients receiving chemotherapy was prolonged by 2 mo, indicating a potential benefit of chemotherapy in the elderly, and so confirming data from studies in the younger population. Adverse events were reversible and of limited impact. The study did not show any grade 4 toxicity, while grade 3 toxicity was verifiable in only 16.4% of cases. Similar encouraging results were reported in trials employing 5-FU continuous infusion (c.i.), which decreases the hematological toxicity. Two Italian phase II experiences evaluated the efficacy and safety of the “de Gramont” schedule in patients aged 70 years or older¹⁸. Both these trials reported ORs in 20% of patients and median survivals of about 12 mo, but demonstrated the feasibility of chemotherapy in elderly patients without quality of life worsening and with improvement of symptoms. In an attempt to anticipate the risks and benefits of chemotherapy, the authors applied the geriatric assessment scales (ADL and IADL) to patients. Unfortunately, neither of these scales was useful to these aims. However, these studies were carried out on a very small sample and there was a high risk of false-negative results. Regarding side effects, gastrointestinal and hematological toxicities were common, but rarely severe. A recent pooled retrospective analysis of data regarding 3825 patients (629 aged 70 years or older) included in 22 European phase II and III trials analyzed the role of 5-FU in the treatment of advanced disease¹⁷. The majority
of elderly patients were aged 70 to 74 years. They were generally treated with bolus 5-FU and its modulation by LV, methotrexate or interferon and less with 5-FU c.i. The results indicated 5-FU-based chemotherapy had the same activity in elderly patients compared with younger subjects, in terms of ORs (23.9% vs 21.1%, respectively; \( P = 0.14 \)), progression-free survival (PFS) (5.5 vs 5.3 mo, respectively; \( P = 0.01 \)) and OS (10.8 vs 11.3 mo, respectively; \( P = 0.31 \)). The 5-FU c.i. allowed a small improvement in these results. Although no significant differences were observed between age and treatment efficacy, the number of subjects over the age of 75 years was only 3.8%. Moreover, elderly patients who entered clinical trials were a select subgroup, with limited comorbidities, and probably not representative of the general older population. Totally absent were the toxicities data in this analysis. Reports on the efficacy and toxicity of 5-FU-based chemotherapy for that group of patients defined as “frail” are lacking in literature.

**Raltitrexed**

Raltitrexed is a nonfluoropyrimidine thymidilate synthase inhibitor that has shown efficacy and tolerability in the treatment of CRC. A randomized trial for metastatic disease demonstrated equal efficacy of raltitrexed compared with a conventional 5-FU-bolus regimen in terms of OR and OS\(^{18}\). However, leukopenia and mucositis were more frequent in the 5-FU-based arm than in the experimental arm. The once-every-3-wk dosing, tolerability profile and ease of administration advocated for further investigation in elderly population. However, 50% of raltitrexed is excreted by the kidney. In the case of renal dysfunction and creatinine clearance decreasing, the dose of drug has to be adapted. The higher rate of therapy-associated deaths due to a failure to adapt the raltitrexed dose in patients with renal dysfunction accounts for the premature closing of the Pan-European Trial on Adjuvant Colon Cancer (PETACC 1)\(^{19}\). The use of raltitrexed may be justified in subjects with 5-FU-associated cardiotoxicity\(^{20}\). As older patients are more likely to have a cardiovascular disease, and patients with pre-existing cardiovascular disease are more likely to experience 5-FU-associated cardiotoxicity, the use of raltitrexed in this age group may be of potential benefit. Two studies have evaluated the efficacy, safety and toxicity of raltitrexed in patients aged 70 years and older\(^{21,22}\). Treatment with raltitrexed resulted in clinical improvement of tumor-associated symptoms in 38% of cases and was associated with an acceptable toxicity profile. In particular, a risk group for nausea-vomiting and diarrhea was females between 70 to 75 years old, and a risk group for liver toxicity was males aged > 75 years. On the basis on these results the authors suggested raltitrexed was a suitable option in elderly patients.

**UFT**

UFT combines the dihydropyrimidine dehydrogenase (DPD) inhibitor uracil with the 5-FU prodrug tegafur in a 4:1 molar ratio. Uracil competes with 5-FU for DPD and inhibits the degradation of the 5-FU generated by tegafur\(^{23}\). Compared with 5-FU alone, administration of UFT results in higher concentrations of 5-FU in tumors\(^{24}\).

Two large, multinational phase III trials compared UFT plus LV versus the Mayo regimen of 5-FU and LV in patients with previously untreated advanced CRC. A regimen of UFT (300 mg/m\(^2\) per day) plus oral LV (75 or 90 mg per day) for 28 d every 5 wk was compared with 5-FU (425 mg/m\(^2\) per day) plus LV (20 mg/m\(^2\) per day) intravenously for 5 d every 4 wk or 5 wk\(^{25,26}\). The larger study with 816 patients reported similar OR rates (12% for UFT plus LV vs 15% for 5-FU plus LV) and no statistically significant difference in survival times. In the second study, which included 380 patients, the two regimens demonstrated similar times to disease progression, median survival times and RR. However, in both studies, the UFT plus LV regimen showed significantly lower toxicity, with a lower incidence of grade 3 mucositis, myelosuppression, febrile neutropenia, and infections, and no notable hand-foot syndrome. These advantages make this form of oral therapy suitable for elderly patients. So, two Spanish groups reported good tolerability and efficacy for the use of UFT in elderly patients with metastatic CRC\(^{27,28}\). A recent ECOG trial evaluated the RR and toxicity profiles of elderly subjects, defined as those \( \geq 75 \) years of age, treated with UFT and LV\(^{29}\). Treatment was administered as UFT (100 mg/m\(^2\)) plus LV (30 mg) every 8 h for 28 d with 7 d of rest. Fifty-eight patients were enrolled with a median age of 81 (range, 75-89). Fifty-seven patients were evaluable for toxicity with grade 3-4 as follows: Gastrointestinal 20 (34%), neutropenia 4 (7%), no hand-foot syndrome. There was only one case of grade 4 diarrhea reported. In six cases (10%), a dose reduction for gastrointestinal toxicity was required, while there were 2 fatalities with gastrointestinal bleeds. The RR was 19%, median time to progression (TTP) was 19 wk, and OS was 11.8 mo. Thus, UFT + LV was well tolerated in this study with an incidence of grade 3-4 toxicity similar to phase III reports in younger patients. Activity was comparable to intravenous 5-FU/LV. This oral fluoropyrimidine is well tolerated and very active in elderly patients.

**Capecitabine**

Capecitabine, an oral formulation of 5-FU, was developed as an alternative to intravenous 5-FU. Compared with the parenteral compound, capecitabine provides greater tumor selectivity while minimizing systemic exposure. The drug is well absorbed via the gastrointestinal tract and is catalyzed to active drug by a series of three enzymes. Over 70% of the metabolites are excreted by the kidney. This makes one cautious when it is necessary to treat an elderly subject. A moderate restriction in liver function does not appear to alter the pharmacokinetic of this drug in a clinically relevant fashion\(^{30}\). A large, randomised, open-label phase II trial conducted in Europe, North America and Australia evaluated three schedules of capecitabine (continuous, intermittent and intermittent with oral LV) in patients with metastatic CRC\(^{31}\). The addition of LV seemed to increase the incidence of side-effects without any benefit to RR or survival times. The RR for the three schedules ranged from 21% to 24%; the median time to disease progression ranged from 127 d to 230 d, with the longest TTP being seen in the capecitabine intermittent arm (with-
This schedule, which consists of twice-daily dosing for 14 d followed by 7 d’s rest, was further evaluated in two phase III trials. Each of these large trials included more than 600 patients. In the trial conducted in 61 centers in the USA, Brazil, Canada, and Mexico, a total of 605 patients were randomized to receive either 2500 mg/m² per day capecitabine in divided daily doses for 14 d followed by 7 d’s rest or the Mayo regimen described above[35,36]. Capecitabine was more active than 5-FU in the induction of a tumor response, and the two groups showed similar times to tumor response and response durations. TTP and OS times were comparable between the two regimens, but the toxicity of capecitabine was less than that of 5-FU, with a substantially lower incidence of diarrhea, stomatitis, nausea and alopecia. However, capecitabine was associated with a higher incidence of palmar-plantar erythrodysesthesia. While capecitabine was shown to be tolerable by fit elderly patients, until a short time ago information on dosing and scheduling for older patients with impaired organ function was not available. Recently, a multicentre phase I/II trial of capecitabine (2000 mg/m² per day for 14 d every 3 wk) was conducted in 214 patients aged ≥ 65 years and/or with an ECOG PS ≥ 1[36]. In the 192 patients evaluable for toxicity, there were no grade 3-4 hematological toxicities. Grade 3-4 toxicity occurred in 22% of patients during the first 3 cycles (8.9% HFS, 6.3% diarrhea, 2.6% leucopaenia, 2.6% dehydration, 1% abdominal pain, 0.5% stomatitis). Dose reductions were required in 14% and dose delays in 21% for medical reasons. In the 151 evaluable for activity, a response was seen in 13%, median PFS was 5.1 mo, and median OS was 16.3 mo. The authors demonstrated lower dose capecitabine was tolerable and active in less fit patients. This study provides valuable information on possible outcomes in these under-studied patients for whom combination chemotherapy may not be preferred. Oral therapies avoided central access devices, with their attendant costs, inconvenience to patients and potential for costly and morbidity complications. These factors, along with patient preference for an oral regimen, have contributed to the development of oral 5-FU preparations.

Irinotecan

Irinotecan (CPT-11) is a semisynthetic derivative of the natural alkaloid camptothecin, and belongs to a new class of antineoplastic agents called topoisomerase I interactive compounds. Since its introduction into the clinic, CPT-11 has undergone a comprehensive evaluation as a single agent and in combination chemotherapy in first-line as well as in second-line therapy of CRC. In two studies using either infusional or 5-FU bolus regimens, CPT-11 was able to improve the objective RR as well as the median survival of patients receiving 5-FU plus LV and CPT-11 combination therapy[42,43]. However, the inclusion criteria of both trials prevented patients over 75 years of age from being treated within the protocol. CPT-11 used as a single agent is associated with equal toxicity in younger and fit older patients (above 65 years of age)[44]. Pharmacokinetic studies have demonstrated equivalent drug pharmacological parameters in patients below or above 75 years of age[45]. A retrospective analysis compared toxicity and survival according to age during a CPT-11-based treatment of 339 patients with flurorpyrimidine-resistant advanced CRC. All patients commenced CPT-11 at 350 mg/m² once every 3 wk and of the 339 patients, 72 (21%) were aged ≥ 70[46]. There were no differences in the proportions of patients developing toxicities by age (< 70 vs ≥ 70: 37.8% vs 45.8%; P = 0.218). Patients aged ≥ 70 had similar ORs (11.1% vs 9.6%; P = 0.585) and survival (median 9.4 vs 9 mo; P = 0.74) compared with younger patients. These data suggest elderly patients derive the same benefit without experiencing more toxicity with second-line CPT-11 treatment for advanced CRC, and do not support the recommendations to give reduced starting doses to elderly patients. Although in a phase II study older patients were twice as likely (38.6% vs 18.8%; P < 0.008) to develop grade 3-4 diarrhea compared with younger patients[47], and although clinicians often reduce the dose of CPT-11 from 350 mg/m² to 300 mg/m² when administered in a three-weekly schedule or from 125 mg/m² to 100 mg/m² in the weekly schedule, this is rather a precaution than an evidence-based indication. Moreover, a recent small retrospective study has demonstrated irinotecan (80 mg/m²) is active and tolerable when administered once a wk for 2 wk, followed by a wk rest in pretreated CRC patients aged 70 years or more[41]. The most frequently observed severe toxicities were diarrhea (grade 3, 13%) and neutropenia (grade 3, 30.4%; grade 4, 8.6%). Only one case of neutropenic fever occurred. Other hematological and non-hematological toxicities were mild and manageable. Objective partial responses (PR) were observed in 13% of cases and an additional 43% of patients reported a stable disease (SD). Just the lack of exhaustive data in literature has justified some recent trials evaluating the efficacy and safety of CPT-11 in combination regimens in elderly patients. In an Italian phase I/II trial accepting pretreated older patients, irinotecan in combination with oxaliplatin (OXIRI) were evaluated through a weekly schedule[48]. Twenty-one patients were enrolled at the second dose level with the maximum tolerated doses of 40 mg/m² for oxaliplatin and 60 mg/m² for CPT-11. The obtained results demonstrated the feasibility of chemotherapy with a good toxicity profile and acceptable efficacy (RR 28%). A Spanish phase II study evaluated the combination of CPT-11 and 5-FU 48 h c.i. as a first-line chemotherapy for patients older than 72 years[49]. Inclusion criteria such as Karnofsky > 70, adequate hepatic and renal function, normal blood cell counts and absence of geriatric syndromes were required. Although treatment delay was observed in 39.7% of cases, particularly for hematological toxicity, and dose reduction was required in 19% of subjects both for hematological and non-hematological toxicity, grade 3-4 toxicities appeared in about 20% of cases. Peripheral venous thrombosis was reported in 4 cases, central venous catheter thrombosis in one case and pulmonary embolism in yet another one. There were 2 toxic deaths, one due to grade 4 diarrhea and acute renal failure and the other due to a pulmonary embolism reported as unrelated to the treatment. Forty-four patients were assessable for efficacy with a RR of 31.8%. Thirty consecutive, previously untreated patients (76 years median age) with metastatic CRC, were
enrolled in another phase II trial evaluating the FOLFIRI regimen\[44\]. Although this combination appeared manageable (grade 3-4 neutropenia 20%; grade 3 thrombocytopenia 3.3%; grade 3 asthenia 10%; grade 3-4 diarrhea 17%), one treatment-related death due to neutropenic sepsis was registered. Overall, RR was 36.6% and the median TTP was 7 mo. After a median follow-up period of 17 mo, the median OS was 14.5 mo. A combined analysis of 2691 patients included in randomized trials has been recently presented to compare the efficacy and toxicity in older (≥ 70 years) and younger (< 70 years) subjects receiving first-line 5-FU/FA with or without irinotecan\[40\]. There was no imbalance regarding risk factors (ECOG PS, WBC, number of tumor sites, alkaline phosphatase and LDH) between elderly and younger patients. Older and younger patients had significantly improved RRs and PFS with combination therapy than with 5-FU/FA. Younger patients had significantly longer OS with irinotecan and 5-FU/FA (P = 0.0003), while older patients had a trend to longer OS with this combination therapy (P = 0.15). The combination was associated with more grade ≥ 3 toxicity in the general population, but there were no significant differences regarding toxicity between older and younger patients. Although this analysis has considered patients aged over 70 years who were selected for inclusion in phase III trials, it has demonstrated elderly patients derive similar benefits from irinotecan-containing chemotherapy, and with similar risks of toxicity, compared with younger patients. Two studies reported preliminary data on the efficacy and tolerability of CPT-11 in combination second-line regimens in patients aged ≥ 66\[46,47\]. The first of these was conducted adopting a weekly schedule of CPT-11 and bolus 5-FU in 10 patients who had relapsed or had progressive disease after oxaliplatin-5-FU/LV combination. Three of the 10 patients showed a PR. The median TTP and median survival time were 4.5 and 12 mo, respectively. However, the toxicity profile was burdened with these percentages of grade 2-3 adverse events: Neutropenia 50%, thrombocytopenia 22%, anemia 33%, diarrhea 33%, nausea 44% and fatigue 39%. The second trial evaluated the safety and efficacy of CPT-11 plus capecitabine. The 26 enrolled patients received first-line chemotherapy with FOLFOX4 in 16 cases, FOLFIRI in 4, and 5-FU/LV/methotrexate in 6 cases. Eight of 24 evaluable patients (33%) showed a response to treatment, median TTP was 5.5 mo, and OS was 11.5 mo. The most common grade 3 side effects were diarrhea (40%), nausea and vomiting (20%), and hand-foot syndrome (10%). Grade 3-4 neutropenia was seen in 40% of patients. No treatment-related death was reported. Nevertheless, more data on the use of CPT-11 in elderly patients would be reassuring.

**Oxaliplatin**

Oxaliplatin is a novel platinum derivative and the first platinum compound to demonstrate significant efficacy in the treatment of advanced CRC. *In vitro* and *in vivo* preclinical studies on CRC have shown oxaliplatin is active against colorectal cell lines and is synergistic with 5-FU\[48\]. In one randomized trial, accepting patients below the age of 75 years, the role of oxaliplatin in combination with 2-d administration of high-dose LV plus 5-FU bolus and low-dose infusional 5-FU in the first-line therapy of advanced CRC was evaluated in 420 patients\[39\]. The objective RRs in elderly and younger patients treated with infusional 5-FU/LV (22.2% vs 21.4%, respectively) were not different from those treated with infusional 5-FU/LV plus oxaliplatin (50% vs 50%; > 65 years, n = 160) as compared to younger patients, respectively. In general, compared with younger patients, this group of elderly patients did not experience increased toxicity except for grade 3-4 diarrhea (18% vs 8%, P = 0.34). The combination regimens employing oxaliplatin plus infusional 5-FU/LV have less hematological toxicity, in particular for FOLFOX2 and FOLFOX6. Thus, clinicians have had a preference for oxaliplatin compared with CPT-11 when they have considered possible the evaluation of a polychemotherapy for elderly patients in several recent phase II studies. An Italian study assessed the tolerability and efficacy of FOLFOX2 in the treatment of pretreated and metastatic elderly patients in comparison to a series of patients < 65 years\[40\]. The preliminary data suggested FOLFOX2 had comparable activity between the two groups (RR 30%) and this schedule was well tolerated in the elderly group. The main toxicities, albeit of short duration, were neutropenia, mucositis, diarrhea, and neurotoxicity. A tailored regimen including capecitabine and oxaliplatin (XELOX) for treating elderly patients with metastatic CRC was planned on September 2001\[41\]. Thirty-five patients aged 70-81 years were treated with an alternated dose escalation for both drugs over the first 3 cycles for each patient in the absence of WHO grade ≥ 2 toxicity on previous cycle. Starting doses were 85 mg/m\(^2\) for oxaliplatin on d 1, and 2000 mg/m\(^2\) for capecitabine, which was taken orally, twice a day, from d 2 to d 15. Dose escalation was performed in 51% of patients for oxaliplatin, and in 11% of cases for capecitabine. No grade 4 and 10 (29%) cases of grade 3 toxicity of any type were reported. Abdominal symptoms (pain, nausea or vomiting) affected 66% of patients, but they were of grade 3 in only 2 patients. Grade 3 diarrhea occurred in 9% of patients. The overall RR was 40%, while PFS and OS time were 6.9 and 14.1 mo, respectively. The authors reported compliance was fairly good considering only one patient went off for refusal in this study. Another three studies have investigated the XELOX regimen as first-line treatment for elderly patients with CRC\[42,43\]. Even if there was one treatment-related death for diarrhea in two of these trials, the authors emphasized the tolerability of this regimen for elderly patients. Thus, in the Felu et al experience, reporting a median relative dose intensity of 92% for oxaliplatin and 98% for caspactain with a RR of 36% and a TTP of 6.9 mo, the more frequent grade 3-4 toxicities per patient were: Diarrhea 22%, asthenia and vomiting 14%, nausea 10%, and anorexia 8%\[43\]. In the Comandone et al trial employing the same combination, 27 patients, 8 of whom were pretreated with chemotherapy, entered the study\[37\]. Following the RECIST criteria the authors observed a RR of 19.2%, while the median TTP and OS were 6.1 and 14.2 mo, respectively. The grade 1-2 toxicities were: Peripheral neuropathy 40%, nausea-vomiting 18%, neutropenia 26%, and asthenia 35%. In
In many patients with CRC. Addition of cetuximab to growth factor receptor (EGFR), which is expressed compromising objective RR or survival being well tolerated with acceptable toxicity without 3 neuropathy and vomiting. The authors recommended 24.3% and 13.5% of patients, respectively. There were no effect was grade 1-2 anemia and neutropenia, observed in 3-4 toxicities were: Neutropenia 32%, diarrhea 10%, and bone marrow function were included. Cetuximab (400 mg/m² as initial dose and 250 mg/m² weekly thereafter) was administered until progressive disease, unacceptable toxicity or consent withdrawal. Only two patients required dose reduction of cetuximab due to toxicity, and there was a dose delay of one wk in 12 cases (29%), achieving a median relative dose intensity of 80%. The main toxicities were those expected for cetuximab: Acne-like rash grades 1-2 (54%), grade 3 (10%), nail toxicity grades 1-2 (7%) and infusion related toxicity grades 1-2 (5%). Thirtynine patients were evaluable for efficacy: One showed a complete response (CR), 5 showed a PR, 15 showed SD, 18 showed progressive disease (PD), resulting in an overall RR of 15.4% and tumor growth control of 54%. Cetuximab monotherapy is feasible in elderly patients as a first-line treatment for metastatic CRC with a favourable safety profile. Response and disease control rates remain in the range observed in pretreated patients. Further research with cetuximab in combination therapies is warranted in this population, as it could improve the efficacy of chemotherapy without jeopardizing its toxicity.

**Bevacizumab**

Bevacizumab is the recombinant humanized version of a murine anti-human vascular endothelial growth factor (VEGF) monoclonal antibody A46.1. One randomized phase III trial utilized a regimen of irinotecan, bolus 5-FU, and FA with or without bevacizumab in patients with a good ECOG PS (PS 0 or 1). This study demonstrated statistically significant and clinically relevant improvements in RR, TTP and survival in the bevacizumab-containing arm. Median survival was increased by 4.7 mo (15.6 vs 20.3 mo; P < 0.001). However, retrospective analyses suggested the benefit derived from irinotecan in chemotherapy combination regimens might be limited to patients with a PS of 0. Also, certain subgroups, including elderly patients, may experience significant toxicities when adding irinotecan to 5-FU/FA regimens. So, a second, supportive, placebo-controlled, randomized, phase II trial was conducted concurrently with the above-mentioned trial in patients deemed non-optimal candidates for first-line irinotecan-containing regimens. Patients had a median age ≥ 70 years, ECOG PS 0 or 1, serum albumin ≥ 35 g/dL, or prior abdominal/pelvic radiotherapy. Subjects were randomly assigned to 5-FU/FA/placebo or 5-FU/FA/bevacizumab. When compared with patients treated with 5-FU/FA alone, the addition of bevacizumab prolonged median survival by 3.7 mo, PFS by 3.7 mo, response duration by 2.4 mo, and increased the RR by 11%. Despite this higher-risk population, the regimen of 5-FU/FA/bevacizumab seemed to be well tolerated. Grade 3 hypertension was more common with bevacizumab treatment (16% vs 3%), but was controlled by oral medication and did not cause study drug discontinuation. No increase in grade 3 or 4 bleeding

**NOVEL BIOLOGICAL AGENTS**

**Cetuximab**

Cetuximab is a monoclonal antibody against the epidermal growth factor receptor (EGFR), which is expressed in many patients with CRC. Addition of cetuximab to chemotherapy improved outcomes both in previously treated and in untreated patients. Only one study has evaluated the activity and safety of cetuximab as a single agent in the first-line treatment of elderly patients. Forty-one patients ≥ 70 years old with confirmed metastatic CRC, Karnofsky PS ≥ 80, and adequate renal, hepatic and bone marrow function were included. Cetuximab (400 mg/m² as initial dose and 250 mg/m² weekly thereafter) was administered until progressive disease, unacceptable toxicity or consent withdrawal. Only two patients required dose reduction of cetuximab due to toxicity, and there was a dose delay of one wk in 12 cases (29%), achieving a median relative dose intensity of 80%. The main toxicities were those expected for cetuximab: Acne-like rash grades 1-2 (54%), grade 3 (10%), nail toxicity grades 1-2 (7%) and infusion related toxicity grades 1-2 (5%). Thirtynine patients were evaluable for efficacy: One showed a complete response (CR), 5 showed a PR, 15 showed SD, 18 showed progressive disease (PD), resulting in an overall RR of 15.4% and tumor growth control of 54%. Cetuximab monotherapy is feasible in elderly patients as a first-line treatment for metastatic CRC with a favourable safety profile. Response and disease control rates remain in the range observed in pretreated patients. Further research with cetuximab in combination therapies is warranted in this population, as it could improve the efficacy of chemotherapy without jeopardizing its toxicity.
or venous thrombotic events was seen in bevacizumab-treated patients. The authors also reported an imbalance in the incidence of arterial thrombotic events: 10% in the 5-FU/FA/bevacizumab group compared with 4.8% in the 5-FU/FA/placebo group. The more advanced age of the population may have contributed to a higher overall incidence of this adverse event.

However, additional research is needed to clarify the appropriate dosing and scheduling of various combination chemotherapy regimens (containing specifically irinotecan or oxaliplatin) plus bevacizumab in older patients.

**CONCLUSION**

Almost half of the CRC cases diagnosed occur in patients over the age of 70. In spite of the fact systemic chemotherapy is beneficial for patients with metastatic disease in terms of survival prolongation, symptomatic improvement and QoL, there is clear evidence that elderly patients are under-treated and under-represented or even excluded from clinical studies. Among the relevant trials for the treatment of CRC patients, probably no more than 20% of cases belong to the over 70 age-group. Nevertheless, elderly CRC patients have been shown to tolerate chemotherapy as well as younger patients in palliative settings with similar RRs. New studies are mandatory to establish particularly the safety of various combinations plus or minus biological agents in older patients. In this context, the results of a randomized phase II study evaluating the activity and safety of capecitabine in combination with oxaliplatin (CAPOX) or with irinotecan (CAPIRI) in patients ≥ 70 years could be of interest. Preliminary data from this trial confirm both combinations are active (RR 38.4% for CAPIRI and 32.2% for CAPOX) with median response durations of 8.2 mo for CAPIRI and 6 mo for CAPOX. The most frequent severe toxicities were diarrhea (CAPIRI: 19.3%; CAPOX: 14.2%) and neutropenia (CAPIRI: 22.5%; CAPOX: 2.8%). No treatment-related death occurred. These findings seem to support the employment of capecitabine given in doublet combination is feasible in elderly patients apart from specimen of the above-mentioned regimens.

Even though the data reported in this review have to be interpreted with caution as these results apply to patients who fulfilled the protocol requirements, age alone is not a sufficient reason to reduce the dose of drugs or to withhold adjuvant or palliative treatment from an elderly patient. The PS is probably not the best mean to estimate the conditions of elderly patients and they need more attention regarding their functional, social and mental status. The main problem which remains to be solved is the applicability of these results to all in the elderly population. Until now, specific studies on unfit older patients are very few or lacking in the literature.

**APPENDIX**

The information was gathered from extensive PUBMED searches (no limits to publication period were applied, but only English language papers are referenced). Additional references, including congress abstract presentations, are included where appropriate and in particular when there are no published studies on a discussion topic.

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