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Elderly colorectal cancer patients are under treated

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Abstract

As the elderly increase as a percentage of the total population the number of elderly patients is also likely to represent an increasing proportion of the total number of colorectal cancer patients (CRC) treated. There is already clear evidence that elderly CRC patients ($\geqslant$ 70 years) are under treated and under represented in clinical trials although it is clear from the results of recent trials that the exclusion of elderly patients from clinical studies is not warranted. In selected patients, without serious co-morbidities and a good performance status, chemotherapy is well tolerated with an efficacy similar to that seen in younger patients. However, physicians need new scales to evaluate changes in function, mental health, nutrition, co-morbidity and quality of life in these patients. Importantly, not only does there need to be a willingness on behalf of the clinician to treat the elderly but also a willingness on the part of the elderly to be treated. These issues will be discussed in the light of the new data available relating to the elderly and to elderly CRC patients in particular.

Keywords: Colorectal cancer; Comprehensive geriatric assessment; CPT-11; Elderly; Irinotecan

1. Introduction

Life expectancy and the incidence of colorectal cancer (CRC) continue to rise in the Western world. Faced with such an aging population, there is likely to be an increase in the number of elderly CRC patients presenting for treatment. In Europe in the year 2000, there were 362,710 new cases of CRC and 198,778 deaths from CRC [1]. The incidence of CRC begins to rise over the age of 40 years and rises sharply to peak in patients aged between 80 and 90 years of age. Almost half the CRC cases diagnosed occur in patients over 70 years of age. Nowadays the life expectancy for a man who reaches 70 is a further 10 years and for women a further 15 years. However, despite the evidence that chemotherapy prolongs survival [2,3], there is clear evidence that elderly patients are under treated and under represented in clinical trials. Among the relevant trials for the treatment of CRC probably less than 20% of patients belong to the over 70 years age group [4].

This is because very often older age is considered to be an exclusion criterion and older patients are associated with an increase in health-related problems. Certainly, elderly patients are associated with an age-related decrease in organ function such as diminishing glomerular filtration rates and urinary excretion, a reduction in plasma proteins, haematopoietic precursors, a decline in mucosal renewal and diminished cardiac and neurologic function, a higher frequency of chronic illness requiring multiple medication and inadequate social or family support, all of which contribute to potentially higher toxicity and the necessity for more careful patient management. Elderly CRC patients with good performance status (PS) have been shown to tolerate 5-fluorouracil (5-FU)-based therapy as well as younger patients in adjuvant [5–9] and palliative [5,10] settings, with similar

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response rates. However, co-morbidity and functional status are important considerations when determining therapy in these patients. Patients with poor function are at an increased risk of toxicity and the life expectancy of these patients is determined by their co-morbidity status. As a consequence guidelines have recently been developed for the treatment of older patients with cancer [11] which involve a geriatric assessment. Chen and colleagues [12] have recently published the results of their prospective pilot study which evaluated the changes in functional, mental, nutritional and co-morbidity status as well as quality of life (QoL) in geriatric oncology patients receiving chemotherapy. There are many scales for Comprehensive Geriatric Assessment (CGA) (Table 1). Elderly patients need to be well supported socially, but finally their life expectancy depends on their co-morbidity status. Generally elderly patients can be divided into three groups as outlined in Table 2.

Currently, as outlined above, there is clear evidence in both adjuvant and palliative settings to support the use of 5-FU-based therapy in patients who can tolerate cytotoxic treatment. These are generally the patients in groups 1 and 2 (Table 2). Although to date few studies in elderly patients with advanced colorectal cancer have been published and the majority of them involve 5-FU therapy, efforts are being made to perform prospective studies in the elderly on the use of 5-FU in combination with newer agents such as irinotecan (Campto®, CPT-11) and oxaliplatin (Eloxatin®) [13,14].

Table 1
Summary of the measurements made during geriatric assessment of the elderly

Comprehensive geriatric assessment	
Function	PS, activities of daily living, instrumental activities of daily living
Health	Number of co-morbidities (Charlson index)
Cognition	Mini-mental status
Depression	Geriatric depression scale
Nutrition	Mini-nutritional assessment
Pharmacy	Polypharmacy
Socio-economic status	Income, education, living conditions, caregiver
Geriatric syndromes	Dementia, incontinence, failure to thrive, neglect and abuse

Table 2
Classification of patients into three treatment categories based on comprehensive geriatric assessment

Group	Description	Treatment
Group 1	Healthy, good PS	Standard treatment
Group 2	Partially dependent, $\leqslant 2$ co-morbidities	
	• Life expectancy shortened by cancer	
	○ if can tolerate treatment	Standard treatment
	○ if cannot tolerate treatment	Palliation
	• Life expectancy not shortened by cancer	Palliation
Group 3	Frail patients who are totally dependent with $\geqslant 3$ co-morbidities or 1 geriatric syndrome	Palliation

2. Current data on irinotecan in elderly patients

2.1. Retrospective analyses

In order to evaluate prognostic factors for survival and particularly age retrospective analyses of the individual data on patients included in two phase III trials, one of irinotecan monotherapy second-line (V-302) [15] and the other irinotecan first-line in combination with infusional 5-FU/folinic acid (FA) (V-303) [16], have been conducted [17,18].

2.1.1. Factors predictive for survival

Univariate and multivariate analyses were performed on the data for 602 patients: 256 patients from the V-302 Rougier trial [15] and 346 patients from the V-303 Rougier trial reported by Douillard and coworkers [16], to determine the factors that were predictive for progression free survival (PFS) and overall survival (OS) [17]. Three factors were independently associated with a better PFS. These were weight loss <5% (HR = 1.25; [95% CI 1.00–1.58]), WHO PS0-1(HR = 1.28 [95% CI 1.08–1.54]) and irinotecan-containing regimen (HR = 1.48 [95% CI 1.03–2.13]). Five factors were independently associated with improved OS. These were: weight loss <5% (HR = 1.67 [95% CI 1.29–2.14]), WHO PS 0-1 (HR = 1.88 [95% CI 1.27–2.75]), $\leqslant 2$ metastatic sites (HR = 1.24 [95% CI 1.01–1.53]), alkaline phosphatases $\leqslant 2 \times$ normal (HR = 1.71 [95% CI 1.30–2.24]) and irinotecan-containing regimen (HR = 1.31 [95% CI 1.07–1.61]). Neither PFS nor OS was associated with patient age. The number of elderly patients ($\geqslant 65$ years) in each arm of each trial are summarised in Table 3. The upper age limit for both trials was $\leqslant 75$ years.

2.1.2. Age is not a prognostic factor for toxicity and efficacy of the combination irinotecan/5-FU/FA

A second analysis performed on 145 patients, treated with irinotecan in combination with the de Gramont infusional 5-FU/FA regimen, in the first-line combination trial [16] to evaluate the tolerability, efficacy and survival by age in patients <65 years (92 patients) *vs.* patients aged 65–75 years (53 patients), showed that there was no significant difference in the occurrence of adverse events between patients greater or less than 65 years of age except for febrile neutropenia which

Table 3
Summary of efficacy data: Proportion of patients ⩾ 65 years [17]

V-302/V-303 retrospective analysis				
	Patients	65–75 years	PFS (mo)	OS (mo)
V-302 trial				
Irinotecan	127	35	4.2	10.8
LV5FU2/AIO	90	29	3.0	7.9
V-303 trial				
LV5FU2/AIO +irinotecan	199	75	5.7	17.4
LV5FU2/AIO	186	61	4.0	14.1

LV, leucovarian; 5-FU, 5-fluorouracil.

Table 4
Tumour response to irinotecan+5-FU as a function of age [18]

V-303 elderly subgroup analysis			
Tumour response			
	<65 years $n = 92$ (%)	65–75 years $n = 53$ (%)	p
Complete response	2 (2.2)	2 (3.8)	
Partial response	27 (29.4)	17 (32.1)	
Stabilisation	30 (32.6)	23 (43.4)	
Progression	28 (30.4)	7 (13.2)	
Non-evaluable	5 (5.4)	4 (7.5)	
Objective response	29 (31.5)	19 (35.8)	ns

occurred more frequently in the older patient cohort [18]. Furthermore, the efficacy (response rate) was not different between the two groups (Table 4).

These two retrospective analyses demonstrate that age up to 75 years is not an independent predictor of PFS or OS to different chemotherapy regimens, including irinotecan/5-FU/FA, and indicated the importance of extending investigations to include patients beyond this age.

2.1.3. Comparative safety and efficacy analysis in younger, middle-aged and elderly patients

The safety and efficacy of biweekly irinotecan plus IV bolus 5-FU/FA was analysed in 108 patients from the SICOG 9801 trial according to age [19]. Patients were retrospectively divided into three age groups: younger ⩽ 54 years (37 patients), middle-aged 55–69 years (64 patients) and elderly ⩾ 70 years (17 patients). Apart from gender the pretreatment characteristics of the three groups were well balanced. WHO grade three neutropenia and diarrhoea affected 42% and 15% of patients, respectively, without any significant difference between groups. Patients ⩽ 54 years stayed on treatment longer (median 24 *vs*. 14–15 weeks) and received more cycles of therapy (median 9 *vs*. 7 cycles) than the older ones. Interestingly, although the older patients received less chemotherapy, response rates were similar in all three age groups: 38% for younger patients, 34% for middle-aged patients and 35% for elderly patients with median times to progression (TTPs) of 7.4, 8.0 and 5.3 months and median OSs of 13.4, 15.3 and 13.9 months, respectively, suggesting that this combination of irinotecan and 5-FU may also represent a suitable therapeutic option for elderly CRC patients. However, physicians need to minimise the risk of side effects in these patients, particularly neutropenia, and to this end prospective studies employing irinotecan in combination with 5-FU are ongoing. Regarding the duration of treatment in the elderly, a recent study in patients receiving 5-FU de Gramont or Lokich or raltitrexed chemotherapy has shown that 12 weeks of chemotherapy with appropriate retreatment is as effective as treatment to progression, suggesting that planned shorter durations of treatment rather than dose reduction might be effective in the elderly [20]. The authors state that these findings may be extrapolated to regimens with agents such as irinotecan and oxaliplatin.

2.2. Prospective analyses

2.2.1. Results from the Spanish TTD phase II trial of high dose 5-FU continuous infusion plus irinotecan

Irinotecan plus 48-h continuous infusion 5-FU has recently been investigated prospectively by the Spanish TTD group in elderly chemotherapy naïve patients with CRC [14]. Ninety one patients ⩾ 72 years old (median age 77 [range 72–85]) were included. Patients were treated with a bimonthly schedule of irinotecan (180 mg/m^2) plus continuous infusion 5-FU (3 g/m^2). All patients had an ECOG PS of 0 or 1, adequate hepatic and renal function, normal blood counts and an absence of geriatric syndromes. The most frequent co-morbidities were hypertension (46%), diabetes (18%), chronic pulmonary disease (8%) and stable cardiopathy (17%). The most common sites of metastases were liver, lung and lymph nodes.

A total of 919 cycles of chemotherapy were administered (median number of cycles 12 [1–19,21–27]). Eighty-five patients were evaluable for toxicity. The most frequent grade 3/4 toxicity was neutropenia which was reported in 21% of patients. Other grade 3/4 toxicities were: diarrhoea 17% and asthenia 13%. Only one case of febrile neutropenia was recorded. There were two treatment-related deaths: one due to diarrhea and one due to digestive haemorrhage. Eighty-five patients were evaluable for response and yielded an overall response rate of 35% (CR: 3 patients and PR 27 patients) and a median PFS of 8.0 months and a median OS of 15.1 months. Thus, this preliminary analysis suggests that irinotecan in combination with continuous infusion 5-FU is an active treatment with low and manageable toxicity in fit elderly patients. The response appears to be better than that obtained with single-agent fluoropyrimidines and the TTP is similar to that reported for

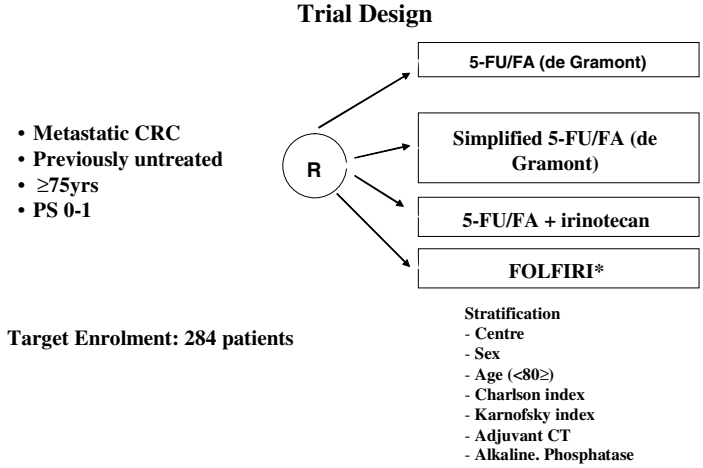

Fig. 1. Prospective FFCD phase III trial of irinotecan in combination with 5-FU/FA in MCRC patients ⩾ 75 years. *, Irinotecan in combination with simplified de Gramont regimen. 5-FU, 5-fluorouracil; FA, folinic acid.

irinotecan/5-FU/FA combinations in mixed age-group patient populations.

2.2.2. Phase III French FFCD trial

Currently, in an ongoing FFCD trial, patients over 75 years are being randomised to four different treatment arms (Fig. 1) and are being stratified according to centre, gender, <80> years, Charlson index (measure of co-morbidity), Karnofsky PS, adjuvant chemotherapy and alkaline phosphatase. The primary endpoint is PFS and the secondary endpoints are response rate (RR), OS, QoL and degree of independence. The planned recruitment is 284 patients. Consistent with the feeling that elderly patients should commence their treatment with a reduced dose of chemotherapy, patients will start their treatment at an irinotecan dose of 150 mg/m^2 for cycles 1 and 2, which depending on tolerance can be increased to 180 mg/m^2 in subsequent cycles. To date this study is open in 72 centres.

2.2.3. Italian study

Daniele *et al.* [21] have already demonstrated that the de Gramont regimen of 5-FU/FA is safe in patients with advanced CRC >70 years of age and have initiated a phase II study of the simplified de Gramont regimen in combination with irinotecan (FOLFIRI) in a similar population of patients. However, in this study patients will be subjected to a multidimensional geriatric assessment using a variety of tools. The principal endpoint of the study is toxicity. As of October 2003, 21 patients had been recruited and only one unacceptable toxicity has been reported, grade 4 neutropenia.

2.2.4. Oxaliplatin- or irinotecan-based therapy for elderly CRC patients

A prospective study of the toxicity and efficacy of oxaliplatin and irinotecan has been conducted in patients >74 years (median age 78 years [range 75–88 years]) [13]. A total of 66 patients were enrolled of whom 39 had no sever co-morbidity according to the Charlson score. Forty-four patients received oxaliplatin and 22 irinotecan in combination with 5-FU/FA or raltitrexed. There were 64 evaluable patients. There were no treatment-related deaths and the authors concluded that in selected elderly patients treatment with oxaliplatin or irinotecan is feasible with manageable toxicity.

3. Current data for oxaliplatin in elderly patients

A retrospective analysis of a randomised trial of patients <75 years of age, all WHO PS 0-2 (>80% PS 0-1) showed there to be no difference in objective RR between elderly patients >65 years of age (160 patients) and those <65 years of age (260 patients) for treatment with infusional 5-FU/FA (22.2% *vs.* 21.4%) or 5-FU/FA plus oxaliplatin (50% *vs.* 50%) [22]. The elderly patient population did not experience increased toxicity except for grade 3/4 diarrhoea (18% *vs.* 8%). However as the two treatment arms were not analysed separately the toxicity of oxaliplatin in combination with 5-FU/FA remains unknown.

The Spanish TTD Cooperative Group is running a phase II trial in elderly (>72 years old) metastatic colorectal cancer patients with high dose 5-FU continuous infusion (3 g/m^2) plus oxaliplatin (85 mg/m^2) every two weeks, until disease progression or unacceptable toxicity. Five patients have been recruited to date.

4. Oral fluoropyrimidines

Increasingly trials of agents for the treatment of advanced and metastatic CRC are including oral

fluoropyrimidines either alone or in combination with other newer agents. Oral capecitabine has been shown to demonstrate clinically meaningful safety advantages compared with IV bolus 5-FU/FA coupled with the convenience of an oral agent [23,24]. Capecitabine is known to be tolerated by fit elderly patients. Dose reductions are required for patients with moderate renal impairment and patients with severe renal impairment should not be treated with capecitabine [25]. In addition, it is known that a moderate restriction in liver function does not appear to affect the pharmacokinetics of this drug in clinically relevant fashion [26].

5. Conclusion

Elderly patients with CRC are clearly under treated and under represented in clinical trials. For the most part, this is because clinicians and patient's relatives perceive old age to be an exclusion criterion. Furthermore, there is a wide variation in the age at which a patient is considered to be elderly. Physiological age can be significantly out of step with chronological age. Clearly elderly patients should be treated, but may require more careful monitoring. The data presented in this review clearly highlight the benefits of using irinotecan-based therapy combined with infusional 5-FU in the treatment of both chemotherapy naïve and previously treated elderly patients. Increasingly there is evidence from the literature that elderly patients want to be treated. A recent study states that more than 70% of elderly patients are willing to receive chemotherapy if there is a reasonable hope of prolonging life, providing that they perceive the treatment to be tolerable [27,28]. Obviously, the treatment to be tolerable [27,28]. Interestingly, there appears to be no survival disadvantage for elderly patients receiving less chemotherapy than younger patients [19]. In addition, chemosensitive patients receiving intermittent therapy fare as well as those treated until disease progression [20], a finding which may extend the patients's therapy options and thus may be applicable for the treatment of elderly patients. Obviously, however, the treatment of elderly patients still has to be assessed on an individual basis, but what is clear is that irrespective of the treatment strategy selected it is very helpful to subdivide elderly patients into the three different classification groups (Table 2), prior to commencement.

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