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ORIGINAL ARTICLE

Chemotherapy compliance, tolerance and efficacy in elderly and non-elderly patients with metastatic colorectal cancer: A single institution comparative study

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Summary

Purpose: *To evaluate whether elderly patients with metastatic colorectal cancer (mCRC) receive chemotherapy of suboptimal intensity and duration, mainly due to fears of poor compliance and/or excessive toxicity.*

Methods: *We carried out a retrospective analysis in a series of 94 mCRC patients. Using the cut-off of 70 years, we compared elderly patients with their younger counterparts in terms of treatment delivery [type, dose intensity (DI), relative dose intensity (RDI), duration], chemotherapy toxicity and efficacy [objective response rate (ORR), overall survival (OS) and progression-free survival (PFS)].*

Results: *Complete data were available for 72 patients (76.6%) among which 38 (52.8%) were elderly. As compared to the younger, elderly patients were more likely to receive single-agent chemotherapy (13.1 vs 0%, p<0.001). The mean number of chemotherapy cycles was 6.2 for the elderly and 8.3 for the non-elderly patients who received either the FOLFOX or FOLFIRI regimen (p=0.142) and 5.1 vs 5.0 for those who received either the XELOX or XELIRI regimen, respectively (p=0.831). In oxaliplatin-containing regimens, elderly patients received 42.8% of the planned dose, as compared to 78.4% for the younger ones (p=0.012). DI for oxaliplatin was higher in non-elderly than in the elderly (46.66 mg/m^2/week vs 32.47 mg/m^2/week, p=0.008). No difference was observed in the rate of severe (grade III-IV) toxicities. ORR, PFS and OS were similar between the two groups.*

Conclusion: *Despite the inferior type and intensity of chemotherapy, elderly patients derived equivalent benefit to their younger counterparts. These data further support the use of optimal chemotherapy in elderly patients with mCRC.*

Key words: *chemotherapy, compliance, elderly patients, metastatic colorectal cancer, toxicity*

Introduction

Cancer mostly affects older patients [1-3] and aging has been proven to be the most important risk factor for carcinogenesis [1]. The chronological timepoint that separates elderly from non-elderly cancer patients is not clearly defined and although there is no consensus [4,5], most of the published trials in oncology use the cut-off of 65 or 70 years for this purpose [6]. However, it is important to note that biological age alone is not the decisive factor that distinguishes the two groups [7]. Moreover, in the last decades a trend has been recorded for less aggressive therapeutic strategy in elderly patients [6,8,9]. Possible explanations for this include the presence of substantial comorbidities, polypharmacy, decreased normal hepatic and/or renal reserves which compromise treatment tolerance, poor compliance, physician's reluctance and barriers in the elderly person's access to medical care [10].

CRC is the most common gastrointestinal tumor in Western countries and its frequency is increasing in elderly patients [11]. Despite the fact that the median age at diagnosis is 71 years and nearly 70% of new cases are over 65 years of age [12], elderly patients are under-represented and often excluded from clinical trials [13,14]. Fur-

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Table 1. Clinicopathological characteristics of the patient population

Characteristics	*Total N (%)*	*Elderly (N=38) N (%)*	*Non-elderly (N=34) N (%)*	*p-value (two-sided)*
Age (years), median (range)	72.0 (34-88)	76.6 (70 – 88)	57.4 (34-69)	
Gender				
Male	45 (62.5)	24 (63.2)	21 (61.8)	NS
Female	27 (37.5)	14 (36.8)	13 (38.2)	
Initial Dukes stage				
B	12 (16.7)	8 (21.1)	4 (11.8)	NS
C	26 (36.1)	15 (39.5)	11 (32.4)	
D	34 (47.2)	15 (39.5)	19 (55.9)	
Grade				
I	6 (8.3)	2 (5.3)	4 (11.8)	NS
II	55 (76.4)	32 (84.2)	23 (67.6)	
III	11 (15.3)	4 (10.5)	7 (20.6)	
Location				
Ascending colon	23 (31.9)	11 (28.9)	12 (35.3)	
Descending colon	9 (12.5)	5 (13.2)	4 (11.8)	NS
Sigmoid	19 (26.4)	8 (23.5)	11 (28.9)	
Rectum	21 (29.2)	11 (28.9)	10 (29.4)	
Adjuvant chemotherapy				
Yes	12 (31.6)	9 (26.5)	21 (29.2)	NS
No	26 (68.5)	25 (73.5)	51 (70.80)	
Surgery				
Yes	28 (73.7)	24 (70.6)	52 (72.2)	NS
No	10 (26.3)	10 (29.4)	20 (27.8)	
Site of metastasis				
Liver	41 (56.9)	22 (57.8)	19 (55.8)	
Lung	30 (41.7)	17 (44.7)	13 (38.2)	NS
Bone	18 (25.0)	9 (23.7)	9 (26.5)	
Brain	7 (9.7)	3 (7.9)	4 (11.7)	
Soft tissue	5 (6.9)	3 (7.9)	2 (5.9)	

NS: non significant

thermore, population-based analyses [8,9] report a trend for suboptimal treatment of elderly patients with CRC, despite the fact that meta-analyses and reports of pooled study populations [11,15] do not suggest different outcomes in terms of toxicity or efficacy.

In order to assess whether elderly patients with mCCR are treated differently from their younger counterparts in the Hellenic clinical setting, we undertook a retrospective analysis of all patients who received first line chemotherapy for CRC in our institution in the last 5 years and compared treatment delivery, tolerance and efficacy between the two age groups.

Methods

Patients

Adult patients with a diagnosis of advanced (recurrent or metastatic) CRC, with measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) [16], with an Eastern Cooperative Oncology Group (ECOG) status of 2 or less, who had received first line chemotherapy between January 2007 and December 2011 were eligible for analysis.

For all eligible patients, we collected clinicopathological data, treatment-related characteristics (chemotherapy regimen, duration, DI and RDI for all administered agents) and information on treatment and patient outcome (ORR, OS, PFS and toxicities). Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria, version 4 (http:/ctep.cancer.gov/protocol/ctc.htm#ctc_40). DI was calculated as the dose delivered per square meter and per week for each chemotherapeutic agent (expressed as mg/m^2/week) and RDI was calculated as the ratio of administered to the planned DI (expressed as percentage) for each pharmacological agent. We opted not to perform analysis on molecular targeted agents [monoclonal antibodies against the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor (VEGFR)] because these agents were not universally available in 2007 and their indications evolved from 2007 to 2011 resulting in a complexity that obscured comparative analysis between elderly and non-elderly patients.

Statistics

Categorical variables were compared in the two study groups with the chi-square test. Continuous variables were analyzed with the Student's t-test or the Wilcoxon test where appropriate. PFS was calculated as the time interval between the date of treatment initiation and the date of documentation of disease progression or death, whichever came first. OS was calculated as the time interval between the date of treatment initiation and the day of death or the last follow-up visit for patients alive at the time of the study completion. Survival curves (PFS and OS) were plotted using the Kaplan-Meier method and compared between the two study groups with the log rank test. A p value < 0.05 was considered statistically significant.Data were analyzed using SPSS version 17.1.

Results

Treatment delivery and adherence

Among 94 patients who fulfilled the inclusion criteria, complete data were available for 72 (76.6%) patients. Using the cut-off of 70 years, 38 (52.8%) patients were assigned to the elderly and 34 (47.2%) to the non-elderly group of patients. Median age of the whole cohort was 72.0 years (range 34-88). There were no significant differences regarding basic clinicopathological variables between the two groups (Table 1). Only 5 (6.9%) patients received monochemotherapy with either 5-fluorouracil or capecitabine while the rest (93.1%) received various combination regimens implementing either irinotecan or oxaliplatin (FOLFOX, FOLFIRI, XELOX, XELIRI). As compared to their younger counterparts, elderly patients were more likely to receive single-agent chemotherapy (13.1 vs 0%, p<0.001). The mean number of chemotherapy cycles for patients treated with either FOLFOX or FOLFIRI was 6.2 for the elderly and 8.3 for the non-elderly (p=0.142), while the corresponding values for the patients who received either XELOX or XELIRI were 5.1 for the elderly and 5 for the non-elderly (p=0.831).

Mean DI for oxaliplatin was significantly lower in the elderly population compared to non-elderly patients (32.47 mg/m^2/week vs 46.66 mg/m^2/week, respectively; p=0.008). Consequently, RDI for oxaliplatin was 42.8% for the elderly and 78.4% for the non-elderly patients (p=0.012). Mean DI for irinotecan was 62.81 mg/m^2/week for the elderly and 69.62 mg/m^2/week for the non-elderly patients (p=0.165). Corresponding RDIs for irinotecan were 52.8% and 62.7% respectively (p=0.170) (Table 2). As for molecular targeted agents included in the chemotherapy regimens (cetuximab, panitumumab, bevacizumab), the small number of patients treated with these agents in our cohort did not allow safe conclusions to be drawn regarding their comparative use in the two age groups of patients.

Table 2. Dose intensity and relative dose intensity for oxaliplatin and irinotecan

		Non-elderly	*Elderly*	*p-value (two-sided)*
Oxaliplatin N=15	DI (mg/m^2/week)	46.66	32.47	0.008
	RDI (%)	78.4	42.8	0.012
Irinotecan N=49	DI (mg/m^2/week)	69.62	62.81	0.165
	RDI (%)	52.80	62.70	0.170

DI: dose intensity, RDI: relative dose intensity

Table 3. Toxicity data

Toxicity	*Non-elderly (N=34) N (%)*	*Elderly (N=38) N (%)*	*Total (N=72) N (%)*	*p-value (two-sided)*
Neutropenia	3 (8.8)	1 (2.6)	4 (5.6)	NS
Anemia	1 (2.9)	0 (0)	1 (1.4)	NS
Thrombocytopenia	1 (2.9)	1 (2.6)	2 (2.8)	NS
Peripheral neuropathy	2 (5.9)	2 (5.3)	4 (5.5)	NS
Diarrhea	3 (8.8)	1 (2.6)	4 (5.5)	NS
Skin rash	1 (2.9)	0 (0)	1 (1.4)	NS
Fatigue	0 (.0)	1 (2.6)	1 (1.4)	NS

NS: non significant

Treatment tolerance and toxicity

The most frequent non-hematological grade 3-4 toxicities were diarrhea (5.5%), peripheral neuropathy (5.4%), skin rash (1.4%) and fatigue (1.4%). Four patients discontinued chemotherapy due to unacceptable toxicity (two with grade 4 diarrhea, one with grade 4 diarrhea and grade 3 fatigue, and one with grade 3 diarrhea and grade 3 rash). Regarding hematological toxicities, grade 3-4 neutropenia was reported in 4 (5.6%) patients and grade 3-4 thrombocytopenia in 2 (2.8%) patients. Severe anemia (grade 3) was noted in one non-elderly patient (2.9%), requiring blood transfusions. There were no significant differences in terms of overall and severe (grade 3-4) hemato-

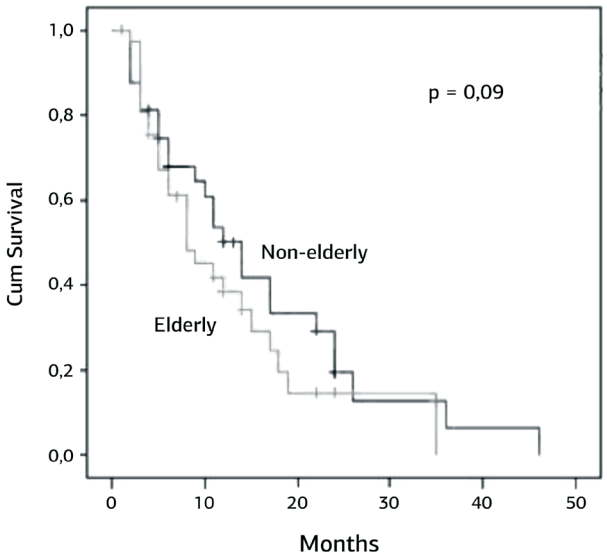

Figure 1. Cumulative progression-free survival according to age group. Non-elderly, median 12.8 months; elderly, median 9.3 months.

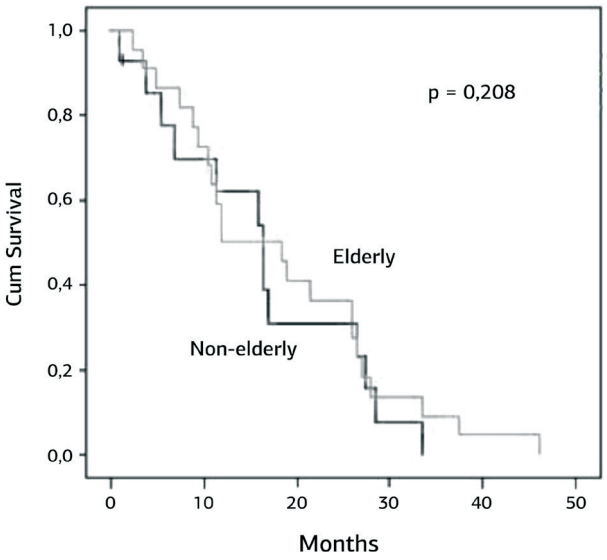

Figure 2. Cumulative overall survival according to age group. Non elderly, median 25 months; elderly, median 24.7 months.

logical and non-hematological toxicities between the two groups of patients (Table 3).

Efficacy

Overall ORR, including complete response (CR), partial response (PR) and stable disease (SD) was 63.8%. Among the responders, 22 were elderly (57.9% of the elderly population) and 24 non-elderly (70.5 of the non-elderly population; p>0.05).

Median PFS for the whole study population was 11 months (95% CI: 8.84-13.16). As compared to their younger counterparts, elderly patients experienced shorter PFS, albeit not significant (median: 9.3 vs 12.8 months, p=0.09). Kaplan Meier curves for PFS are depicted in Figure 1.

Median OS for the whole study population was 24.9 months (95% CI: 18.4-30.9). The corresponding values were 24.7 months (95% CI: 16.3-33.1) for the elderly patient cohort and 25.0 months (95% CI: 16.0-34.1) for the non-elderly patient cohort (p=0.208). Kaplan Meier curves for OS are depicted in Figure 2.

Discussion

More than half (52.8%) of the patients belonged to the elderly group (age at study entry more than 70 years). Given the fact that in most clinical trials in advanced CRC, elderly patients are under-represented, constituting approximately 25-35% of the whole study populations [15,17], our cohort provides a suitable field for comparison of the two age categories. We found that, compared to their younger counterparts, elderly patients were more likely to receive single-agent chemotherapy with either 5-fluorouracil or capecitabine, a fact that might have compromised treatment efficacy and therefore therapeutic outcome. Regarding treatment duration, there was a trend for shorter treatment among elderly patients who were treated with the FOLFOX and FOLFIRI regimens, although this difference did not reach statistical significance, which may also have impacted the therapeutic outcome.

Of note, dosing and frequency of oxaliplatin administration were significantly lower in the elderly group of patients, resulting in suboptimal intensity and duration of treatment with this agent in the same age group. This may be attributed to the recognized toxicities of oxaliplatin and mainly sensor peripheral neuropathy, which is a main concern, especially in elderly patients with a history of diabetic neuropathy. The fact that such a difference was not observed for irinotecan suggests a better tolerance of irinotecan, as compared to oxaliplatin, in elderly patients with advanced CRC.

In the present study, the criterion used for dichotomizing the study population was strictly chronological (cut-off at 70 years of age). The elderly patient population, however, is highly heterogeneous with respect to the patient general performance status, the presence of co-morbidities. It has been suggested that "fit" elderly patients may be offered the same treatments as the ones used in younger patients. On the contrary, less intensive or no chemotherapy should be preferred for more "frail" patients [15]. In either case,

individual functional reserve and life expectancy (regardless of cancer's prognosis), which could affect treatment decisions, might best be evaluated in older patients by a comprehensive geriatric assessment. This takes into account various sides of functionality and health, including mental status, emotional status/depression, activities of daily living (ADLs), instrumental ADLs, home environment, social support, comorbidities, nutrition and polypharmacy [7,18].

Despite the lower intensity and duration of chemotherapy in the elderly patient population, the number of patients that responded to first-line chemotherapy was similar in the two groups of patients (57.9 vs 63.8% for the elderly and non-elderly, respectively), suggesting that elderly patients may also derive substantial clinical benefit from chemotherapy and should therefore not be a priori excluded from intensive chemotherapy protocols applied to the non-elderly population. Of note, a pooled analysis [15] of 22 European clinical trials, including 629 patients with advanced CRC aged ≥70 years at diagnosis, showed that efficacy of chemotherapy, in terms of response rate and OS did not differ significantly in elderly and non-elderly patients. In our study the absence of negative influence of age on chemotherapy efficacy was in accordance with reports from smaller cohorts in both first line and adjuvant settings [19-24]. Moreover, retrospective series and subset analyses [12] show that "fit" older patients derive benefit from optimum multimodality strategies similar with their younger counterparts with no significant difference in toxicity. FOCUS2, an open-label, prospective randomized study [25], was designed to investigate reduced-dose chemotherapy options and to seek objective predictors of outcome in "frail" patients with mCRC. This study showed that, using an appropriate design, frail elderly patients can participate in a randomized controlled trial. A combination including oxaliplatin was preferable to single-agent fluoropyrimidines, whereas capecitabine did not improve quality of life compared to fluorouracil.

In our study no significant differences in severe (grade 3-4) hematological and non-hematological toxicities were noticed between elderly and non-elderly patients. Although this may be, at least in part, attributed to the lower intensity and duration of chemotherapy in the elderly patients, one may postulate that no life-threatening toxicities appear when intense chemotherapy protocols for mCRC are applied in elderly patients.

In conclusion, our data suggests that elderly patients in good general health could and should be offered chemotherapy with the same regimens as those used in younger patients and should be included in the same clinical trials. Thus, elderly patients should not be left untreated or undertreated because of the misperception that they will have greater toxic effects, will have poor tolerance to chemotherapy and will not adhere to the treatment protocol. Elderly patients represent a substantial portion of the whole patient population with advanced CRC and should be offered equal therapeutic opportunities as their younger counterparts in order to derive substantial clinical benefit from available treatment options.

References

1. Khasraw K, Marx G. Chemotherapy in the elderly. Cancer Forum 2008;32: 131-152.
2. Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. Cancer 1997;80:1273-1283.
3. Yancik R, Ries LA. Aging and cancer in America: demographic and epidemiologic perspectives. Hematol Oncol Clin North Am 2000;14:17-23.
4. Pallis AG, Karampeazis A, Vamvakas L et al. Efficacy and treatment tolerance in older patients with NSCLC: a meta-analysis of five phase III randomized trials conducted by the Hellenic Oncology Research Group. Ann Oncol (2011)doi: 10.1093/annonc/mdq772
5. Balducci L. Geriatric oncology: challenges for the new century. Eur J Cancer 2000; 36: 1741–1754.
6. Wedding U, Honecker F, Bokemeyer C, Pientka L, Höffken K. Tolerance to Chemotherapy in Elderly Patients With Cancer. Cancer Control 2007; 14: 44-56.
7. Kohne CH, Folprecht G, Goldbegr R, Mitry E, Rougier P. Chemotherapy in elderly patients with colorectal cancer. The Oncologist 2008;13:390–402.
8. Jessup JM, Stewart A, Greene FL et al. Adjuvant chemotherapy for stage III colon cancer: implications of race/ethnicity, age, and differentiation. JAMA 2005;294:2703-2711.
9. Sundararajan V, Hershman D, Grann VR et al. Variations in the use of chemotherapy for elderly patients with advanced ovarian cancer: a population-based study. J Clin Oncol 2002; 20:173-178.
10. Mortimer J. Cancer in the elderly. ASCO Medical Oncology Self Evaluation Program, 2nd edition, 2010,

445.

11. Berardi R, Saladino T, Mari D et al. Elderly patients with advanced colorectal cancer: Tolerability and activity of chemotherapy. Tumori 2005; 91: 463-466.
12. Emperador PE, Marques EP, Orduna VA. Treatment of metastatic colorectal cancer in the elderly. Cancer Chemother Rev 2011;6: 154-159.
13. Saif MW. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer. Ann Gastroenterol 2012;25: 1-2.
14. Saif MW. Lichtman SM. Chemotherapy options and outcomes in older adult patients with colorectal cancer. Crit Rev Oncol Hematol 2009;72:155-169.
15. Folprecht G, Cunningham D, Ross P et al. Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: A pooled analysis of clinical trials. Ann Oncol 2004; 15:1330 –1338.
16. Eisenhauer EA, Therasseb P, Bogaert J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) Eur J Cancer 2009;45:228 –247.
17. Lewis JH, Kilgore ML, Goldman DP et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003; 21: 1383–1389.
18. Balducci L, Extermann M. Management of cancer in the older person: A practical approach. The Oncologist 2000;5:224 –237.
19. Popescu RA, Norman A, Ross PJ et al. Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older. J Clin Oncol 1999; 17: 2412–2418.
20. Jacobson SD, Cha S, Sargent DJ et al. Tolerability, dose intensity, and benefit of 5FU-based chemotherapy for advanced colorectal cancer (CRC) in the elderly. A North Central Cancer Treatment Group (NCCTG) study. Proc Am Soc Clin Oncol 2001; 20: 587 (abstr).
21. de Gramont A, Bosset JF, Milan C et al. A randomized trial comparing monthly low-dose leucovorin/fluorouracil bolus with bimonthly high-dose leucovorin/fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. J Clin Oncol 1997; 15: 808–815.
22. Weh HJ, Zschaber R, Braumann D et al. A randomized phase III study comparing weekly folinic acid (FA) and high dose 5-fluorouracil (5-FU) with monthly 5-FU/FA (days 1–5) in untreated patients with metastatic colorectal carinoma. Onkologie 1998; 21: 403–407.
23. Kohne CH, Wils J, Lorenz M et al. Randomized phase III study of high dose 5-fluorouracil given as a weekly 24 hour infusion with or without leucovorin vs. bolus 5-fluorouracil plus leucovorin in advanced colorectal cancer. J Clin Oncol 2003; 21: 3721–3728.
24. On behalf of the Advanced Colorectal Cancer Meta-analysis Project: Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 1992; 10: 896–903.
25. Seymour MT , Thompson LC, Wasan HS et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet 2011;337:1749-1759.