Palliative Treatment for Elderly Patients with Colon Cancer in Ten Italian Medical Oncology Units

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Abstract. *Background: Palliative chemotherapy significantly reduces mortality in patients with stage IV colon cancer, but is less prescribed with rising age. In this paper, we highlight the pattern of palliative treatment and possible effects on survival among elderly patients. Patients and Methods: From January to December 2004, 78 files on the management of stage IV colorectal cancer (CRC) patients over 70 years, collected from 10 Italian Centres, were retrospectively examined. Determinants of receipt of palliative chemotherapy and their relation to toxicity and survival were considered. Results: The proportion of elderly patients receiving first-line palliative chemotherapy was 98.7% and it was evaluated according to age, gender, educational level and comorbidities; patients receiving second-line therapy comprised 47.4%, those receiving third-line therapy 14.1% and those treated with a fourth-line therapy totalled 2.6%. Forty-one percent of patients received best supportive care (BSC) alone. Conclusion: In Italy, a proportion of elderly patients with metastatic chemonaive CRC are usually treated with a tolerability and overall survival similar to those for the younger population. Among progressive patients after second-line therapy, 45.8% usually undergo third line therapy; the remaining 54.2% undergo BSC.*

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The prognosis of patients undergoing resection for stage IV colorectal cancer (CRC) remains relatively poor. Palliative treatment has a significant positive effect on survival. The median survival time (MST) is in fact 24 months for patients receiving palliative therapy, as compared with 6 months for those undergoing best supportive care (BSC) alone ($p<0.001$) (1-3). No significant interaction is usually observed between age and the efficacy of treatment (1-3). Several trials have established 5-fluorouracil (5FU)-based chemotherapy plus oxaliplatin and/or irinotecan (CPT11), with or without biological agents, as the standard palliative treatment for patients with stage IV disease (4-7), however, retrospective analyses have shown such chemotherapy to be administered less with increasing age. Moreover, the presence of comorbidity, higher refusal rates among elderly patients, hospital volume and socio-economic factors are reported to influence administration of palliative chemotherapy (8).

In order to evaluate the tolerability of treatment in oncogeriatric patients receiving cancer chemotherapy, the Authors evaluated the colon cancer care of elderly people in 10 Italian Oncology Units, determining the proportion of patients receiving palliative chemotherapy even if in the presence of comorbidities. We assessed factors associated with receipt of chemotherapy and determined to what extent these factors were related to toxicity and survival.

Table I. *Characteristics of 78 elderly patients with stage IV CRC.*

Characteristic		No.	%
Age	Median (range) years		
	≥70 to 75	37	47.5
	>75 to 84	41	52.5
Gender	Male	48	61.5
	Female	30	38.5
Educational level	Primary school	47	60.2
	Middle school	21	27.0
	Secondary school	7	9.0
	University graduate	3	3.8
Hospital centre	Milan	16	20.5
	Padua	14	17.9
	Como	10	12.8
	Borgomanero	8	10.2
	Rome	8	10.2
	Brindisi	7	8.9
	Venice	5	6.5
	Terni	5	6.5
	Novara	5	6.5
Performance status (PS)			
	0	44	56.4
	1	25	32.0
	2	7	9.0
	3	2	2.6
Comorbidities (Charlson's grade)	0	47	60.2
	1-2	21	26.9
	3-4	7	8.9
	5-7	3	3.8

CRC: colorectal cancer; No.: number.

Table II. *Treatment characteristics of all patients.*

Characteristic	No.	%
Most common first-line regimens (77 pts)		
OXA-based	42	54.5
CPT-based	8	10.4
Other	27	35.1
Most common second-line regimens (38 pts)		
OXA-based	12	31.6
CPT-based	20	52.6
Other	6	15.8
Most common third-line regimens (11 pts)		
OXA-based	2	18.0
CPT-based	4	36.4
Other	5	45.6
Most common fourth-line regimens (2 pts)		
CPT-based	1	50.0
Other	1	50.0
Best supportive care (BSC)		
At diagnosis	1	3.1
After:		
first-line therapy	9	28.1
second-line therapy	13	40.7
third line-therapy	7	21.9
fourth-line therapy	2	6.2

pts: patients; No.: number.

Patients and Methods

Eligibility criteria. From November 2005 to May 2006, an open questionnaire concerning the number of metastatic CRC elderly patients over 70 years old in care in 2004, the clinical activity organization for older patients, the opinions on the use of antitumour drugs, granulocytic and erythropoietic growth factors, administration methods, family role, presence of a reliable caregiver and social support, among others, was sent to 10 Medical Oncology Units in Italy. The following patient characteristics were recorded: age at time of diagnosis, gender, serious comorbidities, (according to a slightly modified version of the Charlson classification (9)), Karnofsky performance score (PS) and cognitive status (Table I). Only 11.5% patients underwent multidimensional geriatric assessment (MGA) (10). All conditions incompatible with adequate compliance to the treatment (such as geographical distance, severe hearing and visual defects, dementia) were accurately indicated. Albumin and creatinine values were evaluated.

The questionnaire was forwarded to the Heads of the Units with an accompanying letter from the past International Society of Geriatric Oncology (SIOG) President. The questionnaires were sent back in the following 3 months. On the deadline at the end of May 2006, 78 completed files on palliative chemotherapy from stage IV colorectal adenocarcinoma patients were collected for analysis.

The following tumour characteristics were recorded: tumour grading (low or G1 grading, well or moderately differentiated or G2, versus high grading or G3, poorly or undifferentiated tumours), extent of disease (T1/T2, T3, T4) and lymph node involvement (N1, N2) according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours (sixth edition) (11), site and number of metastases, symptoms.

Prevision of palliative chemotherapy (yes versus no and reasons for why in addition to information on type and dose were available) or BSC were also recorded.

The vital status of all patients on 15 May 2006 was assessed through the Registry Office of different Communes where deceased persons in Italy are registered. At that time, 57 patients (73.1%) were confirmed as still alive.

Objectives. The primary aim of this observational study was to describe the patterns of presentation of metastatic CRC in elderly patients and to collect data about the actual administration of palliative chemotherapy (proposal, acceptance, terms, tolerability, influence by comorbidities).

Secondary objectives were to evaluate the role of prognostic factors (tumour size, nodal involvement, histologic grading, gross finding, histology, visceral involvement, chemotherapy, serious comorbidities) on toxicity, response and overall survival (OS).

Schedule of evaluations. PS, albumin and creatinine were evaluated at the beginning of any new line of therapy; toxicity, use of haematopoietic growth factors, hospitalisation and therapy delay or reduction of doses were checked at the end of each therapy.

Table III. *Characteristics of 77 elderly patients receiving palliative chemotherapy.*

	Frequency	%	Cumulative frequency	Cumulative %
Gender				
F	30	38.96	30	38.96
M	47	61.04	77	100.00
Age at diagnosis (years)				
60-75	43	55.84	43	55.84
>75	34	44.16	77	100.00
Median 74.7				
Age at the beginning of chemotherapy (years)				
60-75	43	55.84	43	55.84
>75	34	44.16	77	100.00
Median 74.67				
Range 68.2-83.3				
Educational level				
Primary school	46	59.74	46	59.74
Middle school	3	3.90	49	63.64
Secondary school	21	27.27	70	90.91
University graduate	7	9.09	77	100.00
Hospital Centre				
Borgomanero	8	10.39	8	10.39
Brindisi	7	9.09	15	19.48
Como	10	12.99	25	32.47
Milano	16	20.78	41	53.25
Novara	5	6.49	46	59.74
Padova	13	16.88	59	76.62
Roma	8	10.39	67	87.01
Terni	5	6.49	72	93.51
Venezia	5	6.49	77	100.00
Bowel movement				
Irregular	26	33.77	26	33.77
Regular	51	66.23	77	100.00
Onset				
Urgent admission	34	44.16	34	44.16
Symptoms	12	15.58	46	59.74
Incidental	31	40.26	77	100.00
PS				
0	44	57.14	44	57.14
1	25	32.47	69	89.61
2	7	9.09	76	98.70
3	1	1.30	77	100.00
PS				
0	44	57.14	44	57.14
>0	33	42.86	77	100.00
Charlson				
0	47	61.04	47	61.04
1-2	20	25.97	67	87.01
3-4	7	9.09	74	96.10
5-6-7	3	3.90	77	100.00
Charlson				
0	47	61.04	47	61.04
>0	30	38.96	77	100.00
Lymphadenectomy				
Missing =4				
No	8	10.96	8	10.96
Yes	60	82.19	73	100.00
Not reported	5	6.85	13	17.81
Site of primary lesion				
Missing =1				
Colon	56	73.68	56	73.68
Rectum	16	21.05	72	94.74
Sigmoid	4	5.26	76	100.00
Stage of disease				
Missing =6				
1	5	7.04	71	100.00
2a	15	21.13	15	21.13
2b	6	8.45	21	29.58
3b	23	32.39	44	61.97
3c	22	30.99	66	92.96
Grading				
Missing =10				
1	4	5.97	4	5.97
2	47	70.15	51	76.12
3	16	23.88	67	100.00
Macroscopic feature				
Missing =12				
Pervasive	36	55.38	36	55.38
Polypoid	10	15.38	46	70.77
Ulcerative	19	29.23	65	100.00
Site of metastases				
Missing = 2				
Liver	35	46.67	35	46.67
Multiple sites	32	42.67	67	89.33
Lung	8	10.67	75	100.00
CEA				
Missing = 11				
Negative	17	25.76	17	25.76
Positive	49	74.24	66	100.00

Variable	N	Mean	Standard deviation	Minimum	Maximum
Albumin (units)	45	36.680	10.795	19.600	90.000
Creatinine (units)	62	90.026	28.145	23.008	234.000

Analyses. This was a multicenter observational study. All the patients over 70 years of age were required to give written consent to participate in the study, which was approved by the local Ethics Committee in October 2005. The observational rather than interventional nature of the study was based on the fact that patients participating in the study did not undergo any procedure that was specifically established by this protocol and that was not already part of the standard clinical practice; similarly, no information was collected for this study other than that acquired during routine clinical practice.

The status of patients lost at follow-up was checked by phone interview or consultation of municipal registers and survival was computed from the date of diagnosis to that of death of any cause. The Kaplan–Meier method was used to estimate the OS course; differences within variables were performed using the log rank test through the SAS Statistical Package (SAS, release 9.1.3., Cari, NC, USA).

Table IV. *Characteristics of palliative chemotherapy in 77 elderly treated patients.*

	Frequency	%	Cumulative frequency	Cumulative %
Number of CHT lines				
1	38	49.35	38	49.35
2	29	37.66	67	87.01
3	8	10.39	75	97.40
4	2	2.60	77	100.00
First-line drugs				
Cpt	8	10.39	8	10.39
Other	25	32.47	33	42.86
Oxa	44	57.14	77	100.00
Second-line drugs				
Missing =40				
Cpt	20	54.05	20	54.05
Other	5	13.51	25	67.57
Oxa	12	32.43	37	100.00
Tird-line drugs				
Missing =66				
Cpt	4	36.36	4	36.36
Other	5	45.45	9	81.82
Oxa	2	18.18	11	100.00
Fourth-line drugs				
Missing =75				
Cpt	1	50.00	1	50.00
Other	1	50.00	2	100.00
BSC				
No	41	53.25	41	53.25
Yes	31	40.26	77	100.00
Not Reported	5	6.49	46	59.74
Status				
0 - Alive	57	74.03	57	74.03
1 - Dead	20	25.97	77	100.00

Results

Patient characteristics. From November 2005 to May 2006, files of 78 patients (38.5% females, 61.5% males) with stage IV CRC, were assessed. Forty-one percent of patients discovered CRC by chance, 43.6% had a medical emergency, 15.4% were symptomatic. All except 1 patient underwent palliative therapy when metastatic disease appeared (98.7%) (48% of patients had metastases in only 1 site, all the others had ≥2 sites). Palliative chemotherapy was administered to 77 of them, independent of gender, age, educational level, hospital, Charlson's score (0 in 61% patients, 1-2 in 26%, 3-4 in 9.1%, 6-7 in 3.9%), PS (0 in 57.1% patients, 1 in 31.1%, 2 in 9.1%, 3 in 2.6%), albumin and/or creatinine values (Tables I and II).

Treatment was promptly accepted by the majority of the treated patients, but a prolonged discussion with the patient to circumvent initial reluctance was required in 19 cases.

Table V. *Characteristics of first-line chemotherapy in 77 elderly patients.*

	Frequency	%	Cumulative frequency	Cumulative %
First-line precocious interruption				
No	29	37.66	29	37.66
Yes	48	62.34	77	100.00
Causes				
Progression	13	27.08	13	27.08
Patient refusal	6	12.50	19	39.58
General decay	6	12.50	25	52.08
Toxicity	22	45.83	47	97.92
Toxicity and disease progression	1	2.08	48	100.00
Response Rate				
Missing =7				
CR	6	8.57	6	8.57
PD	50	71.43	56	80.00
PR	4	5.71	60	85.71
SD	10	14.29	70	100.00
Subjective experience				
Missing =39				
Good	2	5.26	2	5.26
Bad	1	2.63	3	7.89
Very bad	1	2.63	4	10.53
Tolerable	34	89.47	38	100.00
PS				
0	44	57.14	44	57.14
1	28	36.36	72	93.51
2	5	6.49	77	100.00
Delay				
Missing =3				
Not	47	63.51	47	63.51
Yes	24	32.43	74	100.00
Not reported	3	4.05	50	67.57
Dose reduction				
No	54	70.13	54	70.13
Yes	23	29.87	77	100.00
Haematological toxicity				
Missing =24				
0	15	28.30	15	28.30
1	16	30.19	31	58.49
2	12	22.64	43	81.13
3	10	18.87	53	100.00
Non-haematological toxicity Missing =24				
0	14	26.42	14	26.42
1	18	33.96	32	60.38
2	12	22.64	44	83.02
3	8	15.09	52	98.11
4	1	1.89	53	100.00

Variable	N	Mean	Standard deviation	Minimum	Maximum
Albumin (units)	38	36.053	4.100	29.000	51.000
Creatinine (units)	57	90.095	21.795	53.097	164.000

Table VI. *First-line treatment characteristics (77 pts[1])*.

Characteristic	No.	%
OXA-based	42	54.5
FOLFOX		
FOLFOXIRI		
XELOX		
FOLFOX + PTK		
FOLFOX + UFT		
MUGGIA		
CPT-based	8	10.4
FOLFIRI		
XELIRI		
CPT1 + UFT		
Other	27	35.1
5FU + LV		
XELODA		
XELODA + MMC		
TOMUDEX		

[1]All except one patient (who underwent to BSC) received CHT. pts: patients; No.: number; 5FU: 5-fluorouracil; LV: leucovorin; FOLFOX: 5FU+LV+oxaliplatin; FOLFIRI: 5FU+LV+CPT11; XELOX: xeloda+oxaliplatin; XELIRI: xeloda+CPT11; MMC: mitomicyn C.

Table VII. *Attitude of patients towards treatment*.

Characteristic	No.	%
Initial attitude		
Patient agreement	48	61.5
Patient agreement with initial doubts	19	24.3
Family decision without patient information	10	12.8
No indication	1	1.4
Tolerability to first-line therapy (77 pts)		
Very good	2	1
Good	34	15
Bad	1	1
Very bad	1	1
Not administered	39	20
Tolerability to second-line therapy (38 pts)		
Very good	2.6	2.6
Good	44.1	39.6
Bad	1.3	2.6
Very bad	1.3	2.6
Not administered	50.7	52.6

pts: patients; No.: number.

Table VIII. *Response rate (2 months after the end of CHT)*.

	CR	PR	SD	PD[1]
After first-line therapy (71.4%) (70 evaluable pts)	6 (8.6%)	4 (5.7%)	10 (14.3%)	5 0
After second-line therapy (84.2%) (19 evaluable pts)	0	0	3 (15.8%)	1 6

[1]All the patients who underwent CPT11-based CHT, 68.3% of those who underwent OXA-based CHT and 66.7% of those who underwent other CHT regimen progressed. CHT: chemotherapy; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive

Table IX. *More common toxicities and delay or dose-reduction after first- and second-line therapy.*

	Grade 1-2	Grade 3-4
Toxicity to first-line therapy (77 pts)		
Haematological	28 (36.4%)	10 (12.9%)
Non-haematological		
Diarrhoea	16 (20.8%)	6 (7.8%)
Neurotoxicity	15 (19.5%)	1 (1.3%)
Mucositis	14 (18.2%)	1 (1.3%)
Alopecia	9 (11.7%)	0
Asthenia	5 (6.5%)	1 (1.3%)
Hand foot syndrome	2 (2.6%)	0
Nausea	1 (1.3%)	0
Toxicity to second-line therapy (38 pts)		
Haematological	15 (39.5%)	6 (15.8%)
Non-haematological		
Diarrhoea	10 (26.3%)	4 (10.5%)
Neurotoxicity	6 (15.8%)	0
Mucositis	4 (10.5%)	0
Alopecia	7 (18.4%)	0
Asthenia	2 (5.3%)	1 (2.6%)
Hand foot syndrome	1 (2.6%)	0
Vomiting	1 (2.6%)	1 (2.6%)
	Delay >1 wk	Dose-reduction
First-line therapy	24 (31.2%)	22 (28.6%)
Second-line therapy	12 (31.6%)	17 (44.7%)

Treatment regimens. As first-line therapy, capecitabine alone or in combination with oxaliplatin/irinotecan/or mitomycin C was administered to 29.5% of 77 treated patients; a FOLFOX4 regimen (oxaliplatin plus 5FU by bolus + continuous infusion/leucovorin (LV)) alone or in combination with PTK (a vascular epithelial growth factor receptor tyrosine kinase inhibitor)/or irinotecan was administered to 26.9% patients; oxaliplatin alone or in combination with 5FU/LV/tomudex/or uracil-tegafur (UFT) was administered to 17.9% patients; 5FU/LV was administered to 14.1% patients; a FOLFIRI regimen (irinotecan plus 5FU by bolus + continuous infusion/LV) was administered to 3.8% patients; tomudex alone or UFT plus irinotecan were administered to the remaining patients (Tables III-VI). Similar drugs were administered as second- or third-line therapy.

Twenty-eight patients with Charlson's score 0 (59.6%) received oxaliplatin-based chemotherapy, 6 (12.8%) received

Table X. *Most common toxicities after first-line therapy and common characteristics: statistical significance.*

Haematological toxicity				
	0-2	3-4	Total	*p*-value Fisher's exact test
Age at diagnosis (years)	32	6	38	
60-75				0.7452 (ns)
>75	28	4	32	
Non-haematological toxicity				
Bowel movements				
Irregular	18	6	24	0.0544
Regular	43	3	46	
PS				
0	39	2	41	0.0279
>0	22	7	29	
Grading				
1-2	46	3	49	0.0466
3	11	4	15	

	Toxicity	No.	Median	Range	Wilcoxon *p*-value
Albumin (units)	0-2	34	38.285	24-90	0.0405
	3-4	7	29.814	19-38	

Table XI. *Relationship within hospitalisation and basal PS, creatinine and albumin value.*

	First-line	Second-line	Third-line	Fourth-line
Hospitalisation during CHT	4 (5.2%)	2 (5.3%)	0	0
PS pre CHT				
0	44 (56.4%)	14 (36.8%)	5 (45.4%)	1 (50%)
1	28 (35.9%)	17 (44.7%)	2 (18.2%)	1 (50%)
2	5 (6.4%)	2 (5.3%)	0	0
3	1 (1.3%)	0	1 (9.1%)	0
na	0	5 (13.2%)	3 (27.3%)	0
Albumin value pre CHT (unit)				
<20	0	0	0	0
20-25	0	1 (2.6%)	1 (9.1%)	0
26-30	4 (5.1%)	1 (2.6%)	1 (9.1%)	1 (50%)
>31	34 (43.6%)	20 (52.6%)	5 (45.4%)	1 (50%)
na	40 (51.3%)	16 (42.2%)	4 (36.4%)	0
Creatinine value pre CHT (unit)				
50-70	8 (10.2%)	1 (2.6%)	0	0
70-90	25 (32.1%)	11 (28.9%)	0	0
90-110	17 (21.8%)	7 (18.4%)	5 (45.4%)	1 (50%)
110-130	4 (5.1%)	4 (10.6%)	1 (9.1%)	1 (50%)
>130	3 (3.8%)	4 (10.6%)	2 (18.2%)	0
na	21 (27.0%)	11 (28.9%)	3 (27.3%)	0

CHT: chemotherapy; na: not available.

CPT11-based chemotherapy and the others (27.6%) received other drugs (Xeloda, 5FU/LV, UFT, tomudex, mitomycin C); 11 patients (55%) with Charlson's score 1-2 received oxaliplatin-based chemotherapy, 1 (5%) received CPT11-based chemotherapy and the others (40%) received other drugs (Xeloda, 5FU/LV, mitomycin C); 3 patients (42.8%) with Charlson's score 3-4 received oxaliplatin-based chemotherapy, 1 (14.4%) received CPT11-based chemotherapy and the others (42.8%) received other drugs (Xeloda, 5FU/LV, mitomycin C); all patients with Charlson's score >5 initially received oxaliplatin-based chemotherapy.

Only very few patients received granulocyte (7.8%) and erythropoietic growth factors (2.6%) after first-line therapy; 10.5% and 2.6% patients, respectively, received them after second-line therapy and 14.3% and 14.3%, respectively, after third-line therapy.

Forty-one percent of patients underwent best supportive care (BSC) alone (3.1% at the diagnosis of metastatic disease, 28.1% after first-line therapy, 40.7% after second-line therapy, 21.9% after third-line therapy and 6.2% after fourth-line therapy).

Precocious interruption of chemotherapy was reported in 61.5% patients. In 47.9% of them the first cause was toxicity, in 27.1% progressive disease, in 12.5% general worsening and in 12.5% cases patient refusal (Table VII).

Response, toxicity and PS. Out of 70 patients radiologically assessable for response, only 10 patients (14.3% overall response rate) experienced a partial (PR) or complete remission (CR) after a first-line therapy; 10 patients (14.3%) had stable disease (SD) and all the others progressed (PD) (Table VIII).

Twenty-eight point six percent of first-line cycles, 44.7% of second-line therapy and 50% of third-line therapy were administered at <75% of prefixed dose intensity due to either dose reduction and/or omission (Tables IX and X). Within those 44 patients who received oxaliplatin-based chemotherapy as first-line therapy, 8 (20.4%) had no toxicity; 22 (50%) patients reported a grade 1-2 (G1-2) and 6 (13.6%) a G3-4 haematological toxicity. Within those patients with G1-2 non-haematological toxicity, 2 (4.5%) patients with nausea, 3 (6.8%) with alopecia, 5 (11.4%) with asthenia, 9 (20.4%) with mucositis, 11 (25%) with diarrhoea, 15 (34.1%) with neurotoxicity were reported; G3-4 toxicities were observed in 1 (2.3%) patient with mucositis, 1 with (2.3%) neurotoxicity and 5 (11.4%) with diarrhoea. Within the 8 patients treated with CPT11-based chemotherapy as first-line therapy, 1 (12.5%) had no toxicity; 2 (25%) patients reported a G1-2

and 2 (25%) a G3-4 haematological toxicity. Within those patients with G1-2 non-haematological toxicity, 5 (62.5%) patients with alopecia, 3 (37.5%) with mucositis, 3 (37.5%) with diarrhoea were reported; G3-4 toxicities were observed in 1 (12.5%) with diarrhoea and 1 (12.5%) with asthenia. Within the 25 patients receiving other drugs 14 (56%) had no toxicity; 4 (16%) patients reported a G1-2 and 2 (8%) a G3-4 haematological toxicity. Within those patients with G1-2 non-haematological toxicity 1 (4%) patient with alopecia, 2 (8%) with mucositis, 1 (4%) with diarrhoea, 2 (8%) with hand foot syndrome were reported; G3-4 toxicities were observed in 1 (4%) patient with diarrhoea.

At the beginning of first-line therapy, PS was worse than at diagnosis in 9% patients and at the end of first-line therapy, PS was worse than at the beginning of treatment in other 9% patients (Table XI). A high PS value significantly influenced non-haematological toxicity (p=0.0279). Albumin and creatinine values are reported in Table VII. A low albumin value also influenced non-haematological toxicity (p=0.0405).

The significant relationship between irregular bowel movements at diagnosis (p=0.054) or high grade of disease (p=0.046) and non-haematological toxicity were difficult to explain.

Progression and survival. After first-line therapy, 47.4% patients underwent second-line therapy.

Survival did not seem to depend on TNM (p=0.26), number or site of metastases (p=0.28), site of primary lesion (p=0.45), features of primary lesion (p=0.46), first-line therapy (p=0.44), CEA (p=0.58), age at diagnosis (p=0.08), gender (p=0.98), educational level (p=0.1), PS (p=0.58) or Charlson's score (p=0.22). Only high grading of disease seemed to slightly influence survival (p=0.05).

Again, the reported relationship between irregular bowel movements at diagnosis (p=0.0038) and survival was unaccountable.

Discussion

The accrual to this retrospective observational study was particularly difficult due not only to the absence of complete files about patients coming from different Centres in Italy but also to several problems typical of the elderly such as concomitant comorbidities, patient's refusal of chemotherapy, early dropout of patients, incomplete awareness of disease, absence of a reliable caregiver, logistic limitations or other socio-economic conditions that hampered data (12); 9.1% of patients withdrew early from the therapy and missed the first re-evaluation of disease.

The observational character of this study in which data on clinical benefit and adverse events of different regimens were collected from clinical practices in different Centres helped us to understand the actual feasibility of all kinds of palliative treatments in everyday practice and eliminate the bias of patient selection typical of clinical trials (10) (actually 57% of them had a PS 0 and 61% a Charlson's score of 0, so a minimal selection was probably performed in this case). No significant interaction was observed between age and type of treatment adopted (4-7) or between age and efficacy of treatment (1-3) (p=1.00).

Presence of comorbidity, hospital volume and socio-economic factors did not influence administration of therapy (8). By our analysis, a low refusal rate was reported among patients: 98.7% received, in fact, palliative chemotherapy. The toxicity rate (about 28% of dose reduction after first-line therapy) and MST were similar to those observed among younger patients. Moreover, patients over 75 years of age reported similar haematological toxicity to younger patients (p=0.74); this fact could be another demonstration of the importance to treat patients of all ages without any preconceptions. Within patients receiving oxaliplatin-based chemotherapy as first-line therapy, 20.4% of them had no toxicity and G1-2 and G3-4 haematological toxicity were reported in 50% and 13.6% cases (in contrast to literature data reporting up to 36-42% of G3-4 in younger patients) (7, 13), respectively. Mucositis (20.4%), diarrhoea (25%) and neurotoxicity (34.1%, in contrast to literature data reporting up to 50% of neuropathy) were the more common G1-2 non-haematological toxicities; G3-4 toxicities were unusual (literature data report up to 18-20% of neuropathy). Within patients treated as first-line therapy with CPT11-based chemotherapy, 12.5% had no toxicity. G1-2 haematological toxicity (25%) was less common than that observed with oxaliplatin, while G3-4 toxicity (25%) was worse. Within those patients with G1-2 non-haematological toxicity, alopecia (62.5%), mucositis (37.5%) and diarrhoea (37.5%) were more frequent than those reported after oxaliplatin; G3-4 toxicities were rare. Within patients receiving other drugs 56% had no toxicity; haematological and non-haematological toxicity were uncommon. When oxaliplatin was administered as second-line therapy (12 patients), haematological toxicity was similar to first-line administration; G1-2 neurotoxicity rate increased (41.6%) while mucositis and diarrhoea seemed to be reduced (8.3%). When CPT11 was administered as second-line therapy, G1-2 haematological toxicity was of 35% (better than that observed after oxaliplatin) and G3-4 of 15%; diarrhoea G3-4 was increased (20% of cases) while alopecia and diarrhoea G1-2 (25%, respectively) were less common then in first-line therapy. High PS and low albumin values significantly influenced non-haematological toxicity.

Bowel movements (p=0.0038) and high grading of disease (p=0.05), but not the type of first-line therapy, had a significant positive effect on survival (73% of patients were alive in May 2006). The MST was in fact of 16 months for patients receiving palliative therapy, as compared with 4

months for those undergoing BSC alone (however, data are not sufficient to confirm this result because only 1 patient underwent BSC at diagnosis of disease).

Conclusion

Observational studies can help to understand the actual feasibility of all kinds of palliative treatments in everyday practice and eliminate the bias of patient selection typical of clinical trials (10, 14). Comorbidities should not be a limit to chemotherapy administration; if well studied they could influence a better choice of schedule. According to the obtained results, development of age-based guidelines and increased awareness among both physicians and patients through education may be important to prevent undertreatment of elderly patients who are eligible for chemotherapy. With decision making becoming more individualised with rising age, the use of a comprehensive geriatric assessment may also be helpful in choosing the most adequate treatment for these patients (15-17). Nevertheless, the improved use of granulocyte and erythropoietic growth factors could help them in particular situations even if toxicities seem to be lower in the elderly (according to our data) than in younger patients.

References

1 Yellen SB, Cella DF and Leslie WT: Age and clinical decision making in oncology patients. J Natl Cancer Inst *86(23)*: 1766-1770, 1994.

2 Fratino L, Serraino D, Rossi E, Lonardi S and Monfardini S: Survival of elderly patients with metastatic colorectal cancer is improved by inclusion in phase II trials. IV Meeting of International Society of Geriatric Oncology (SIOG). abstr 74, 2003.

3 Extermann M, Overcash J, Lyman GH, Parr J and Balducci L: Comorbidity and functional status are independent in older cancer patients. J Clin Oncol *16*: 1582-1587, 1998.

4 Saltz LB, Cox JV and Blanke C: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med *343*: 905-914, 2000.

5 Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L and Rougier P: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer. A multicenter randomised trial. Lancet *355*: 1041-1047, 2000.

6 Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y, Coudert B, Bertheaut-Cvitkovic F, Larregain-Fournier D, Le Rol A, Walter S, Adam R, Misset JL and Lévi F: Phase III multicenter randomised trial of oxaliplatin added to chrono-modulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol *18*: 136-147, 2000.

7 De Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F and Bonetti A: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol *18(16)*: 2938-2947, 2000.

8 Lichtman SM and Skirvin JA: Pharmacology of antineoplastic agents in older cancer patients. Oncology (Huntington) *14*: 1743-1755, 2000.

9 Charlson ME, Pompei P, Ales KL and MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis *40*: 373-383, 1987.

10 Basso U and Monfardini S: Multidimensional geriatric evaluation in elderly cancer patients: a practical approach. Eur J Cancer Care *13*: 424-433, 2004.

11 UICC. TNM Classification of Malignant Tumours. Sixth edition. New York: Wiley-Liss *75*: 25-35, 2002.

12 Monfardini S. Prescribing anti-cancer drugs in elderly cancer patients. Eur J Cancer *38*: 2341-2346, 2002.

13 Andre T, Bensmaine MA, Louvet C, François E, Lucas V, Desseigne F, Beerblock K, Bouché O, Carola E, Merrouche Y, Morvan F, Dupont-André G and de Gramont A: Multicenter phase II study of bimonthly high-dose leucovorin, fluorouracil infusion, and oxaliplatin for metastatic colorectal cancer resistant to the same leucovorin and fluorouracil regimen. J Clin Oncol *17(11)*: 3560-3568, 1999.

14 Fentiman I, Tirelli U, Monfardini S, Schneider M, Festen J and Cognetti F: Cancer in the elderly: why so badly treated? Lancet *28*: 1020-1022, 1990.

15 Satariano WA: Comorbidities and cancer. *In*: Cancer in the Elderly. Hunter CP, Johnson KA, Muss HB (eds.). New York, NY: Marcel Dekker Inc pp. 477-499, 2000.

16 Repetto L, Fratino L and Audisio RA: Comprehensive geriatric assessment adds information to Eastern Cooperative Oncology Group performance status in elderly cancer patients: an Italian Group for Geriatric Oncology Study. J Clin Oncol *20*: 494-502, 2002.

17 Extermann M, Overcash J and Lyman GH: Comorbidity and functional status are independent in older cancer patients. J Clin Oncol *16*: 1582-1587, 1998.

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