Adjuvant Treatment for Elderly Patients with Colon Cancer. An Observational Study

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Abstract. *Background: Adjuvant 5-fluorouracil-based chemotherapy significantly reduces mortality in patients with stage II-III colon cancer, but is less prescribed with rising age. In this study we were interested in the pattern of adjuvant treatment and possible effects on survival among elderly patients. Patients and methods: From January to December 2004, 63 questionnaires on the management of stage II-III resected colon cancer patients aged over 70 years, collected from 10 Italian Centres, were retrospectively examined. Determinants of receipt of adjuvant chemotherapy and their relation to survival were considered. Results: The proportion of elderly patients receiving adjuvant chemotherapy was 79.4%, distinct of age, gender, educational level and comorbidities. Grade 3-4 toxicities were the following: haematological in 4 (8.5%) patients, mucositis in 4 (8.5%), diarrhoea in 2 (4.2%) and nausea in 1 (2.1%). The disease-free survival (DFS) and overall survival (OS) at two years were 79.9% and 95.6%, respectively. Due to the paucity of events, the impact of prognostic factors (patient's age and comorbidity, tumour stage and grade) on DFS and OS could not be assessed. Conclusion: An increasing proportion of elderly patients with colon cancer may be treated with a tolerability and OS similar to those observed in the younger population. Development of age-based guidelines and increased awareness of both physicians and patients through education is important to prevent undertreatment of those elderly patients who are eligible for chemotherapy.*

The prognosis for elderly patients who have undergone resection of a stage II-III colon carcinoma remains relatively poor. Adjuvant treatment has a significant positive effect on both overall survival (OS) and time to tumour recurrence ($p<0.001$) (1). The 5-year OS is in fact 71% for patients receiving adjuvant therapy, as compared with 64% for those untreated. No significant interaction is usually observed between age and the efficacy of treatment (1). Several trials have established 5-fluorouracil (5-FU)-based chemotherapy as the standard adjuvant treatment for patients with stage III disease (2-7), however, retrospective analyses have shown such adjuvant chemotherapy to be administered less with increasing age. Moreover, the number of involved nodes, presence of comorbidity, higher refusal rates among elderly patients, hospital volume and socioeconomic factors are reported to influence the administration of adjuvant chemotherapy (1, 8-11).

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

Patients and Methods

Eligibility criteria. From November 2005 to May 2006, an open questionnaire concerning, for example, the number of stage II-III colon cancer patients ≥70 years old in care in 2004, the opinions on the use of antitumour drugs, haematopoietic growth factors,

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Table I. *Questions in the questionnaire.*

General	Adjuvant treatment
Medical Unit	Indication and reasons
Patient-related	Was chemotherapy suggested by the doctor?
General background	Patient informed about disease
Educational level	Comorbidities adequacy to therapy
Profession	PS adequacy to therapy
Physical characteristics	Cognitive functioning adequacy to therapy
Date of birth	Family involvement in the patient's life
Weight	Family agreement to adjuvant chemotherapy
Height	Adequate logistic support
Disease-related characteristics of patient	Chemotherapy administered and reasons why
Blood value of albumin and creatinine	Precocious interruption and causes
Creatinine clearance	Number of cycles
Symptoms at diagnosis	Before any cycle:
Intestinal function	- patient PS
First appearance	- weight
Multidimensional Geriatric Assessment (MGA)	- body surface
Performance Status (PS)	- blood value of albumin, creatinine and cholesterol
Activity of Daily Living (ADL)	- creatinine clearance
Instrumental of Activity Of Daily Living (IADL)	- delay of dose administration
Mental Status (MMS)	- dose reduction and cause
Depressive Geriatric Symptoms (GDS)	- maximal toxicity, neurotoxicity, febrile neutropenia
Comorbidities according to Charlson's classification	- granulocyte growth factors administration
	- erithropoietic growth factors administration
Disease-related	- hospital admission, time and causes
Surgery	Two months after the end of treatment:
Surgery of the primitive lesion and number of resected nodes	- patient PS
Patient's agreement to surgery	- weight
Disease characteristics	- MGA
Date of diagnosis	- personal experience of chemotherapy
Site	- late toxicity
Stage	- relapse local or systemic
Grading	- date of relapse
Macroscopic feature	- site and number of metastases
Vascular involvement	
Lymphatic involvement	Patient status

administration methods, family role, type of support required and patient informed consent was sent to all Medical Oncology Units in Italy (Table I).

The following patient characteristics were recorded: age at time of diagnosis, gender and comorbidity, the latter scored according to Charlson's classification (12). 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 returned in the following 3 months. To send and get back the completed questionnaire took 40 days. By the fixed deadline of May 2006, 63 completed files on adjuvant chemotherapy in stage II-III colon adenocarcinoma forms were collected for analysis.

Colon tumours were defined as C18.0–C18.7 according to International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The following tumour characteristics were recorded: tumour grade (low grade, well- or moderately differentiated, *versus* high grade, poorly or undifferentiated tumours), postoperative extent of disease (T1/T2, T3, T4) and lymph node involvement (N1, N2). The stage II patients were classified into two subgroups (IIA, T3N0; IIB, T4N0); the stage III patients were classified into three subgroups (IIIA, any T1-2/N1; IIIB, T3-4/N1; IIIC, any T/N2)

according to the International Union Against Cancer (UICC) TNM Classification of Malignant Tumours (sixth edition) (13).

Adjuvant chemotherapy (yes *versus* no and reasons for administration in addition to information on type and dose were available) and hospitals where treatment was administered were also recorded.

The status of all patients was assessed by phone interviews or by consultation with Municipal registries.

Statistical analysis. Patient numbers were compared for categorical variables by means of chi-squared test (with Fisher's exact correction for frequencies less than 5). Variables tested for the choice of chemotherapy were gender, age ≤75 *versus* >75 years, Charlson's score (0 *versus* 1-4), tumor stage and tumor grade (G1-2 *versus* G3). Progression was measured from time of surgery to first evidence of local/systemic relapse or death for any cause, while survival was measured from time of surgery to death for any cause. Disease-free survival (DFS) and OS were estimated by means of the Kaplan-Meier method using Statistica software, version 6 (Statsoft, Inc., Tulsa, OK, USA). Prognostic factors for DFS and OS were tested by means of log-rank test.

Results

Ten out of 50 Medical Oncology Units in Italy answered.

Patient characteristics. Sixty-three elderly patients radically resected for colon cancer were identified, with a median age of 76 years (range 70-84 years). Their characteristics are outlined in Table II. Twenty-one patients (33.4%) were asymptomatic at the time of diagnosis, while 11 had anaemia and/or rectal bleeding (17.4%), 22 abdominal pain and/or constipation (34.9%) and 9 had acute complications requiring urgent hospital admission (14.3%). The median creatinine clearance value was 50 ml/min (range 28-97 ml/min). Only 12 patients had been evaluated by means of Multidimensional Geriatric Assessment. Only 1 patient was dependent for one or more Activity Daily Living (ADLs, ability to carry out common daily activities such as washing, dressing, eating, moving), 3 patients were dependent on one or more Instrumental Activity Daily Living (IADLs, ability to carry out common instrumental daily activities such as using money, phone or transport, cleaning, doing the shopping, taking medication) and 10 had a Mini Mental State (MMSE) score >24; 8 patients reported a Geriatric Depression Scale (GDS) <5.

Fifteen patients did not have any concomitant disease, while the distribution according to Charlson's score is outlined in Table II.

Choices concerning adjuvant chemotherapy. According to the treating oncologist, an indication for adjuvant chemotherapy was present in 58 patients, but in 8 cases treatment was not started due either to the patient's refusal (4 patients), family interference, or inadequate support (4 patients). Treatment was promptly accepted by the majority of the 50 treated patients, but a prolonged discussion with the patient to circumvent initial reluctance was required in 6 cases (12%).

Since adjuvant chemotherapy was started in 14 (53.8%) stage II patients and in 36 stage III patients (97.3%, *p*=0.001), the involvement of lymph nodes was confirmed as the most relevant adverse prognostic parameter for actual administration of such treatment. Moreover, among the 26 patients with stage II colon cancer, administration of adjuvant chemotherapy increased according to T stage (50% of patients in T3N0 *versus* 71.4% of patients in T4N0, *p*=0.26) but data were not significantly different (Table III). Males had a nonsignificant trend for an increased percentage of N+ disease (66.7 *versus* 41.1%, *p*=0.14) and the prescription of adjuvant chemotherapy (83.1% *versus* 74.1%, *p*=0.37). Prescription of adjuvant chemotherapy did not correlate either with age ≤75 *versus* >75 years (86.7% *versus* 72.7%, *p*=0.17) or with performance status (PS) 0 *versus* 1-2 (81.8% *versus* 71.0%, *p*=0.72).

Positive lymph nodes were present in approximately half of both subgroups of grade 1-2 and grade 3 tumour patients (55 *versus* 56.5%, *p*=0.9), with almost equal percentages of

Table II. *Patient characteristics (N=63).*

	No.	%
Median age (range)		
76 years (70-84)		
Age group (years)		
≥70 to 75	30	47.6
>75 to 84	33	52.4
Gender		
Male	36	57.2
Female	27	42.8
Performance status (PS)		
0	22	35.0
1	36	57.1
2	4	6.3
3	1	1.6
Comorbidities		
(Charlson's grade)		
0	34	54.0
1	17	27.0
2	3	4.8
3	7	11.0
4	2	3.2
Symptoms		
Yes	42	66.7
No	21	33.3
Site of primary lesion		
Sigma	20	31.7
Colon	39	61.9
Cecum	4	6.4
Stage of colon disease		
II A	19	30.1
B	7	11.1
III A	5	8.0
B	18	28.6
C	14	22.2
Grading of tumour		
1	2	3.2
2	38	60.3
3	23	36.5

prescription of adjuvant treatment (77.5% in grade 1-2 *versus* 82.6% in grade 3, *p*=0.63).

Chemotherapy was administered independently of Charlson's grade of comorbidity (50% of patients without comorbidity score 0 *versus* 63.6% of patients score 1 to 4, *p*=0.21); 69.2% of patients who did not undergo chemotherapy had a Charlson's grade 0.

Type, duration and toxicity of adjuvant chemotherapy. The chemotherapy regimen was based on a combination of 5-FU and folinic acid, with the addition of oxaliplatin in only 5 patients. The mean number of cycles was 5.18 (range 1 to 6).

Grade 3-4 toxicities were: haematological in 4 (8.5.%) patients, mucositis in 4 (8.5%), diarrhoea in 2 (4.2%) and nausea in 1 (2.1%). Granulocytic growth factors were

Table III. *Characteristics of 50 elderly patients who underwent adjuvant chemotherapy.*

Characteristic	No	%
Gender		
Male	30	64
Female	20	36
Performance status (PS)		
0	18	36
1	31	62
2	1	2
Comorbidities (Charlson's grade)		
0	25	50
1	15	30
2	2	4
3	6	12
4	2	4
Stage of colon disease		
II A	9	18
B	5	10
III A	5	10
B	18	36
C	13	26
Grading of tumour		
1	2	4
2	29	58
3	19	38

Table IV. *Treatment compliance within 50 patients who underwent adjuvant chemotherapy.*

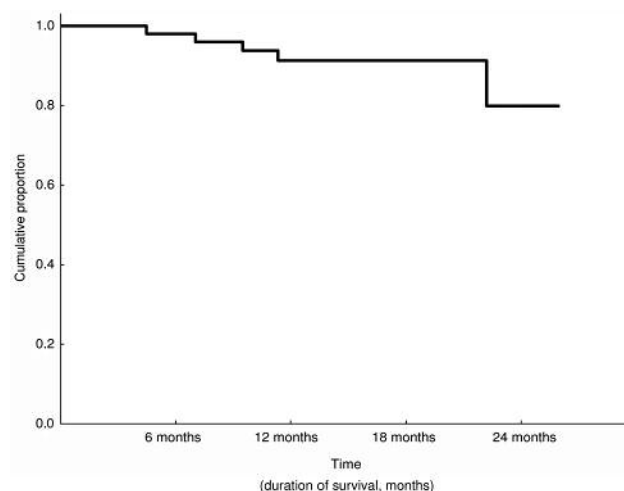|	No.	%
Tolerability		
Good	26	52
Very good	8	16
Bad	6	12
Very bad	10	20

Figure 1. *Disease free survival in 54 evaluable patients (5 events, 49 censored). (duration of survival, months).*

employed in 1 patient, while erythropoietin was administered to 4 patients. There were no episodes of neutropenic fever and no toxic deaths. Heterogeneity of regimens, dosages and incidence of dose reductions does not allow an objective comparison of toxicity according to age, PS and comorbidity score of the patients.

Early interruption of chemotherapy was reported in 14 patients (28%). Treatment-related toxicities were the main cause (11 patients, 78.6%), followed by patient refusal (2 patients) and progression (1 patient). Toxicity-related interruption did not appear to be related to age (5/26 patients ≤75 years old and 6/24 patients >75 years old, p=0.62) or Charlson's score (5/25 with score 0 and 6/25 with score ≥1, p=0.73).

Overall, 34 patients (68%) gave a positive rating for the subjective experience of chemotherapy (Table IV).

Time to progression and survival. At the end of May 2006, follow-up data were available for 54 patients. After a median follow-up of 15.1 months, 5 patients had progressed and 2 had died due to the relapsed tumor. Site of relapses were liver only (2 patients), liver and peritoneum (2 patients) and liver and subcutaneous (1 patient). Three patients underwent metastasectomy, one systemic chemotherapy and two were not treated. The DFS (Figure 1) and OS at two years were 79.9% and 95.6%, respectively.

Due to the paucity of events, the impact of prognostic factors (patient's age and comorbidity, tumor stage and grade) on DFS and OS could not be assessed. Yet all relapsing patients were N2 (2 pT3 and 3 pT4), none of them was grade 1.

Discussion

In our study of 63 patients aged 70-84 years with stage II-III colon cancer, we found that adjuvant chemotherapy was equally administered according to increasing age, gender, PS and comorbidity level. All patients with more than T3N0 stage of disease underwent therapy.

The chemotherapy schedule choice was not influenced by inter-hospital variation.

Toxicity was comparable with published data on adjuvant chemotherapy in elderly patients (diarrhoea 4%; stomatitis 8%; nausea and vomiting 2%) and toxicity-related interruption did not appear to be related to age (p=0.62) or Charlson's score (p=0.73). Overall, 68% of patients gave a positive rating to the subjective experience of chemotherapy (Table IV).

The lower probability of receiving adjuvant treatment for elderly patients with colon cancer has already been shown (8, 9, 14-18). The reason why these patients are less likely to receive adjuvant treatment is multifactorial. In addition to the presence of concomitant diseases, more patient refusal among the elderly, the absence of supportive caregivers, a decrease in the patients' general condition, especially frailty and cognitive abilities, could result in lower chemotherapy rates (10, 19-22). Referral to medical oncology is also one of the most important factors associated with reception of chemotherapy among older patients with stage III colon cancer. Ensuring that high-risk patients are referred to medical oncology is also a crucial step in quality care for patients with colon cancer (11).

Most of the available studies present evidence of tolerance and efficacy of chemotherapy among both selected and unselected elderly colon cancer patients (8, 10, 15, 23, 24), thus counteracting the persisting 'ageism' in colon cancer care. However, there are probably still uncertainties about the risk–benefit ratio of aggressive treatment, as is sometimes suggested by the observed inter-hospital variation (25).

Despite the reported similar tolerance among males and females for 5-FU-based chemotherapy, the higher refusal rate among elderly women may partly be responsible for the finding that the latter were less likely to receive adjuvant treatment (9, 26, 27).

Patients presenting with comorbidities received adjuvant chemotherapy like the other patients, in contradiction with previous retrospective clinical studies (9, 10, 17, 18). Few prospective studies have reported the effect of comorbidity on the safety and efficacy. Our results underline that Italian oncologists are not influenced by comorbidities in their decision-making and this could be an important sign that elderly patients in some centres are not undertreated as often appears in the literature data. On the other hand, only 12 patients had been evaluated by means of Multidimensional Geriatric Assessment; in fact a Multidimensional Geriatric Assessment could be more useful for analyzing single patients and problems better.

Patients with stage IIIB disease (T3–4, N1) received adjuvant chemotherapy as stage IIIC disease (any T, N2); also in this case, the treatment choice was not influenced by age.

Because of the low number of events, it is not possible to say if adjuvant chemotherapy had a marked independent prognostic impact (18, 23). Due to the population-based nature of our data, we do not know the extent to which this positive prognostic impact was caused by selecting the 'fitter' patients for adjuvant chemotherapy, or by other factors (6).

Our finding that patients aged 70 or older had a better prognosis than patients aged 65-69 years is odd, but in line with the results of a large single-hospital study where patients with stage III colon cancer aged 65 years or older had an overall 5-year survival of 74% , compared to 54% for patients younger than 65 years (28). A possible explanation for this finding might be a selection of the more robust individuals living long enough to develop colon cancer, or a potential decrease in aggressiveness of the tumour with rising age.

Data extraction from the patient's medical record is regarded as the most complete source of information on the patient's past and current health status (29). All except two patients with PS ≥2 did not undergo therapy; all the others had a PS of 1. Performance score and comorbidity are usually both predictive factors of treatment and survival for cancer patients, independent of each other (30, 31). However, PS often depends on malignant disease and its treatment, in contrast to comorbidity. In this case, among all patients not undergoing therapy, only one had a Charlson's comorbidity grade 3 (and PS 1), another a grade 2 (and PS 2) and another one a grade 1 (and PS 2).

Although the proportion of elderly patients with colon cancer receiving adjuvant chemotherapy is increasing, many elderly patients still do not receive or accept this treatment.

A total of 13.8% of patients did not undergo chemotherapy due to the patient's refusal (50% of cases), or family interference (50% of cases). In 6 cases (12%), a prolonged discussion with the patient to circumvent initial reluctance was also required. Devoting time to the relatives may also represent a key element in creating a communicative and efficient relationship with older cancer patients (32).

Conclusion

In this everyday setting, results confirm the experience from large multicentric studies: stage III patients are offered adjuvant chemotherapy on a regular basis, while around only 50% of stage II patients are treated. A trend towards treatment in younger and fitter patients or those with T4 tumours was found. Because of the very short follow-up and small sample size, the value of survival curves might be questioned.

Development of age-based guidelines and increased awareness of both physicians and patients through education is important to prevent undertreatment of (subgroups 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 be helpful in choosing the most adequate treatment for these patients.

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