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Raltitrexed in the treatment of elderly patients with advanced colorectal cancer: an active and low toxicity regimen

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Abstract

In spite of the high prevalence of advanced colorectal cancer in the elderly, we have little data on the efficacy and toxicity of chemotherapy in this age group. Raltitrexed is a thymidylate synthetase inhibitor with known activity in the treatment of advanced colorectal cancer. The objective of this study was to analyse the efficacy and tolerance of raltitrexed in elderly patients with advanced colorectal cancer. 92 patients diagnosed with advanced colorectal cancer aged $\geqslant 70$ years were entered into the study. Raltitrexed was given at a dose of 3 mg/m^2 once every 3 weeks for a minimum of three cycles. A total of 511 cycles were given with a median of five cycles per patient. 20 out of the 90 patients evaluable for response achieved a partial response (PR) (22%, 95% Confidence Interval (CI): 17–36%), 43 (48%) remained stable and 27 showed progression (30%). The mean duration of response was 24 weeks and the progression-free interval was 15 weeks. The overall median survival was 41 weeks. 31 patients (39%, 95% CI: 28–50%) experienced a clinical benefit (improvement of the performance status without a worsening of symptoms or relief of symptoms without a worsening of the performance status). The main toxicities were gastrointestinal and haematological. 12 patients (13%) developed grade 3-4 side-effects: 7 had nausea/vomiting (8%), 6 a transaminase increase (7%), 4 asthenia (4%), 3 diarrhoea (3%), 2 neutropenia (2%), 2 anaemia (2%) and 1 thrombocytopenia (1%). Three toxic deaths occurred (3%). The group of patients with a creatinine clearance $\leqslant 1.08$ ml/s was found to have a higher risk of developing grade 3-4 toxicity compared with those with adequate renal function (8/18 versus 4/72; $P < 0.001$). In conclusion, raltitrexed is an active, convenient and low toxicity treatment for the elderly with advanced colorectal cancer. However, it must be used cautiously in elderly patients with a creatinine clearance $\leqslant 1.08$ ml/s since they are at a higher risk of suffering grade 3-4 toxicity. © 2002 Published by Elsevier Science Ltd.

Keywords: Raltitrexed; Colorectal cancer; Elderly; Chemotherapy; Toxicity

1. Introduction

Colorectal cancer is the second most common cause of death from cancer in developed countries [1]. Its incidence increases significantly with age, from 20 cases/100 000 habitants/year in men under 65 years old to 337/100 000 in the elderly [2]. In Europe, 40% of patients are over 74 years old at the time of diagnosis [3]. Furthermore, considering future demography perspectives, the incidence of colorectal cancer will progressively increase.

In spite of the magnitude of the problem, the treatment of colorectal cancer in elderly patients remains a challenge. Several studies have shown that the proportion of

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patients with this tumour who are operated upon decreases with age (85% of patients under 65 years versus 70% of older patients) [4]. Furthermore, chemotherapy treatment is also used less frequently in the elderly compared with other age groups, both in the adjuvant [5] and the advanced settings [6].

A number of factors may account for the reluctancy to use chemotherapy in elderly patients. (1) The limited number of studies analysing the efficacy and toxicity of chemotherapy in this age group [7]. (2) Fear that elderly patients may be more susceptible to suffer side-effects that decrease their quality of life, especially diarrhoea, mucositis and myelosuppression [8,9]. (3) Comorbid conditions, that may complicate or even preclude the administration of chemotherapy [10].

However, it is currently accepted that chemotherapy in patients with advanced colorectal cancer prolongs survival time by 5–6 months compared with best supportive care [11]. The same benefit is also obtained when early treatment in asymptomatic patients is given compared with postponing treatment until the occurrence of symptoms [10]. Furthermore, chemotherapy for advanced colorectal cancer patients has been reported to be effective in maintaining or improving quality of life [10–13]. Although these studies have not specifically been conducted on elderly patients, the benefits might be extrapolated to this age group. The most common treatment has been the association of 5-fluorouracil (5-FU) with leucovorin (LV). However, there is some concern that this combination may induce high toxicity in elderly patients: with some exceptions [10,14] this age group has been reported to have a greater risk of mucositis, diarrhoea, hand–foot syndrome and myelosuppression [8,15], as well as a 9% rate of toxic deaths [8]. These observations were confirmed in a posterior meta-analysis [9]. For that reason, it seems necessary to investigate other regimens that improve the toxicity profile, while maintaining the efficacy of 5-FU-LV.

Raltitrexed (ZD1694) is a thymidylate synthetase inhibitor. This enzyme has a fundamental role in the *de novo* synthesis of the nucleotide thymidine triphosphate, which is essential for DNA synthesis. At a dose of 3 mg/m^2 it is active in a variety of tumours such as breast, pancreatic or refractory ovarian cancers [16], but it is in colorectal tumours where it shows the best activity. Several phase III studies performed in patients with advanced colorectal cancer have demonstrated that its activity is similar to that of the combination 5-FU-LV [17,18]. In a randomisd phase III study that compared 5-FU-LV versus raltitrexed the risk of developing grade 3-4 mucositis and leucopenia was higher in those patients $\geqslant 70$ years who received 5-FU-LV, but not in those treated with raltitrexed [19]. The administration as a short intravenous (i.v.) infusion of 15 min every 3 weeks adds value to the efficacy and toxicity profile of raltitrexed.

In spite of having included patients aged $\geqslant 70$ years in these studies, the experience with the use of raltitrexed in elderly patients is very limited. The objective of the present study was to analyse the activity and toxicity of raltitrexed in elderly patients with advanced colorectal cancer.

2. Patients and methods

2.1. Patient eligibility

Between July 1997 and December 1999, 92 patients with recurrent or metastatic advanced colorectal cancer and aged $\geqslant 70$ years were included. They all had at least one lesion histologically confirmed as adenocarcinoma. The inclusion criteria were: (1) a performance status $\leqslant 2$, according to Eastern Cooperative Oncology Group (ECOG) scale [20]; (2) life expectancy of at least 3 months; (3) adequate medullar function, that is a granulocyte count $\geqslant 2\times10^9$/L and platelets $> 100\times10^9$/L; (4) adequate hepatic function, that is serum bilirubin < 1.25 times the upper normal limit, glutamic oxaloacetic transaminase values (SGOT) and glutamic pyruvic transaminases (SGPT) < 2.5 times the upper normal limit in the absence of hepatic metastases or < 5 times the upper normal limit in the presence of metastasis; (5) adequate renal function, that is a creatinine value $\leqslant 1.25$ times the upper normal limit and creatinine clearance > 1.08 ml/s.

Patients previously treated with chemotherapy were excluded, with the exception of adjuvant chemotherapy that had been finished at least 6 months before. Similarly, patients with cerebral metastases or a history of a previous neoplasia were also excluded, except those with *in situ* carcinoma of the cervix or basal cell carcinoma of the skin.

All the patients had one or more measurable or evaluable lesions in accordance with World Health Organization (WHO) guidelines [21]. Patients treated with radiotherapy were included as long as there was at least one evaluable lesion outside the radiation field.

All the patients gave their written consent according to the directives of the local ethical committees.

2.2. Pretreatment and Follow-Up studies

The diagnostic work-up was performed within 3 weeks prior to the start of the treatment. It consisted of a complete clinical history, physical examination, a blood analysis (haemogram and complete biochemistry) and imaging studies as needed (chest X-ray, computed tomography of the chest, abdomen and pelvis, abdominal echography and bone scan). The Charlson comorbidity scale was used [22]. The ECOG performance status and weight were also recorded. An electrocardiogram (ECG) was performed in all patients prior to the treatment. Symptom assessment, physical examination

and blood biochemistry were repeated before each treatment. The measurements of tumour sizes were performed every three months or sooner if clinically indicated.

2.3. Treatment

Raltitrexed is available as a freeze-dried powder. This product has to be reconstituted with 4 ml of sterile water for injections and then diluted in 50 ml of 5% dextrose or 0.9% saline. The dilution thus reconstituted is administered as a short i.v. infusion for approximately 15 min. The dose of raltitrexed was 3 mg/m^2 once every 21 days. A minimum of three cycles were given unless a progression of the disease was detected. The concomitant use of vitamin complexes containing folinic acid was not allowed. Prophylaxis with antiemetics was prescribed routinely, although the choice of anti-HT3 drugs or metoclopramide depended on the criteria of the physician.

Patients with an objective response or a stabilisation with symptom improvement continued treatment until the occurrence of a progression or unacceptable toxicity. Patients with stable disease and no symptom improvement received six cycles.

Toxicity was recorded before each new cycle and graded according to WHO scales [21]. The administration of chemotherapy was delayed until recovery from toxicity for a maximum of 3 weeks. In the case of grade 3 or 4 haematological toxicity, the dose of raltitrexed was decreased by 25 or 50%, respectively. If grade 2 or 3 diarrhoea occurred, the dose was reduced by 25 or 50%, respectively; grade 4 diarrhoea led to treatment withdrawal.

The Cockcroft–Gault formula [23] was used to calculate creatinine clearance before each cycle. If creatinine clearance was between 0.42–1.08 ml/s, the dose of raltitrexed was reduced by 50% and the next cycle given 4 weeks later. If it was 0.42 ml/s, the treatment was interrupted.

2.4. Definition of response

2.4.1. Response, time to progression, survival

The response was assessed at the end of every three cycles of chemotherapy and carried out following WHO directives [21]. For that purpose, both measurable and non-measurable, but evaluable, lesions were considered. A complete response (CR) was defined as the disappearance of all clinical and radiological evidence of the tumour assessed through physical examination or radiological explorations or both, for a minimum of 4 weeks. A partial response (PR) was defined as a reduction of at least 50% in the sum of the products of the longest perpendicular diameters of the clearly measurable tumour lesions during at least 4 weeks without detecting an increase greater than 25% in any lesion or the occurrence of new lesions. Stable disease (SD) indicated a decrease of less than 50% in total tumour size or an increase of less than 25% in the size of one or more measurable lesions. Progression was considered when an increase of at least 25% in the size of one or more measurable lesions or the occurrence of new measurable lesions was detected. Death occurring before the first assessment of response, caused by the progression of the disease or by toxicity, was considered as a therapeutic failure. Progression-free survival was measured from the start of chemotherapy to the date of progression or death without progression. Survival was calculated from the first day of treatment to the date of death or to the date of last follow-up.

2.4.2. Palliative benefits

ECOG performance status and the symptoms before each chemotherapy cycle were assessed by the same doctor for each patient. The presence of pain, use of analgesics, anorexia and asthenia were registered. Patients went through a pain stabilisation lead-in period to establish baseline measures. Pain was assessed with the Memorial Pain Assessment (MPA) Card visual analogue scale. Asthenia and anorexia were assessed with a visual analogue scale (VAS) of 0–100. In addition, the patient's weight was measured at each visit. It was considered that a patient could be evaluable for palliative benefits when he/she initially had one of the following signs or symptoms: an ECOG performance status $\geqslant 1$, a MPA score $\geqslant 20$, a baseline analgesic consumption of $\geqslant 10$ morphine-equivalent mg/day, a score on the visual analogue scale for anorexia and/or asthenia $\geqslant 20$ or a previous weight loss $> 10\%$ in the previous 6 months.

Symptom improvement was obtained when: (1) there was an improvement in the ECOG performance status by at least one score from baseline; (2) there was a weight gain by at least 5% from baseline. Patients with peripheral oedema, ascites or pleural effusion were excluded from this category; (3) there was an improvement of $\geqslant 50\%$ from baseline in disease-related symptoms (pain, use of analgesics, anorexia and asthenia) and in the analgesics consumption (measured weekly in morphine-equivalent milligrams) compared with baseline. All this improvement had to be sustained for at least 4 weeks [18]. Clinical benefit was defined as: (1) ECOG performance status improvement without worsening of symptoms or weight loss, (2) weight increment without worsening of ECOG or symptoms, (3) symptoms improvement without worsening of ECOG performance status.

2.5. Statistical methods

The dose intensity was calculated for each patient from the total dose of raltitrexed administered during

the entire course of the treatment, and this is expressed as the mean drug dose in milligrams per square metre per week.

Univariable analysis was used to compare the incidence of grade 3-4 toxicity between the different groups formed according to age (above 75 years or not), gender, creatinine clearance (below 1.08 ml/s or not) or Charlson comorbidity scale (0–1 versus $\geqslant 2$).

Wilcoxon rank-sum test was used to compare the quantitative variables and Fisher's exact test for the percentages were used. Survival time and time to progression were calculated using the Kaplan–Meier method.

3. Results

3.1. Patients characteristics

A total of 92 patients with recurrent or metastatic advanced colorectal cancer and aged $\geqslant 70$ years were entered into the study. The characteristics of these patients are shown in Table 1. The median age of the series was 77 years (range 71–88 years). There were 39 patients (42%) aged $\geqslant 76$ years and 12 patients (13%) aged $\geqslant 80$ years. 48 patients were males (52%) and 44 were females (48%). There were 18 patients (20%) with an ECOG performance status of 0, 64 (70%) with 1 and 10 (11%) with 2. In 48 patients (52%), the primary tumour was located in the colon and in 44 (48%) in the rectum. There were 26 patients (28%) who presented with metastasis at the time of diagnosis, in 14 of which (15%) the primary tumour was not resected. 66 of the remaining patients (72%) presented metastases secondary to a tumour previously resected. Of these patients, 38 (41%) had previously received chemotherapy as adjuvant therapy and 25 (27%) had received chemotherapy and radiotherapy. Regarding the symptoms, there were 25 (27%) with a weight loss greater than 10% in the previous 6 months, 38 (41%) with a pain score $\geqslant 20$, 24 (26%) with a baseline analgesic consumption of $\geqslant 10$ morphine-equivalent mg/day, 59 (64%) with asthenia $\geqslant 20$ on the VAS and 76 (83%) with anorexia $\geqslant 20$ on the VAS. Seventy patients (76%) had comorbid conditions, mainly hypertension (25%), obstructive lung disease (17%), ulcer disease (15%), coronary insufficiency (13%) and diabetes (10%). Comorbidity was present in 60% of patients when using Charlson's scale [22]. According to this scale, 32 patients scored one (35%), 19 scored two (21%) and 4 patients equal to or greater than three (4%).

A total of 511 cycles were given with a median of five cycles per patient (range 1–13). 11 patients (12%) received less than three cycles of raltitrexed: 3 (3%) due to toxic death, 4 (4%) due to progression, 2 (2%) due to the patient's refusal and another 2 (2%) due to death apparently not related to the neoplasia (1 due to an acute stroke and another 1 due to an acute myocardial infarction). Except for these last 2 patients, all of the others were considered valid for the toxicity and response analyses. In 15 patients (16%), the treatment had to be delayed on some occasions: 6 due to an increase of transaminases, 3 due to diarrhoea, 2 due to neutropenia, 1 due to thrombocytopenia and another 3 because of the patient's request. The median dose intensity was 0.92 mg/m^2/week (range 0.75–1 mg/m^2/week). 77 patients (84%) received 90% or more of the planned dose.

Table 1
Patients' characteristics

Characteristic	*n* (%)
Age (years) (mean and range)	77 (71–88)
70–75	53 (57)
76–80	27 (29)
>80	12 (13)
Gender	
Male	48 (52)
Female	44 (48)
ECOG Performance Status	
0	18 (20)
1	64 (70)
2	10 (11)
Number of organs with metastasis	
1	62 (67)
2	22 (24)
$\geqslant 3$	8 (9)
Metastatic sites	
Liver	42 (46)
Liver plus others	16 (17)
Lung	20 (22)
Intra-abdominal extension	12 (13)
Lymph nodes	10 (11)
Others	28 (30)
Weight loss	
None	19 (21)
1–10%	48 (52)
>10%	25 (27)
Pain score	
0–19	53 (58)
20–49	28 (30)
50–100	11 (12)
Baseline analgesic requirement (morphine-equivalent mg)	
<10	66 (73)
10–100	18 (20)
>100	6 (6)
Asthenia score	
0–19	33 (36)
20–49	46 (50)
50–100	13 (14)
Anorexia score	
0–19	16 (17)
20–49	43 (47)
50–100	33 (36)

ECOG, Eastern Cooperative Oncology Group.

3.2. Tumour response and survival

Out of the 90 patients valid for response, 20 reached a PR (22%, 95% Confidence Interval (CI): 17–36%), 43 (48%) remained with a SD and 27 showed a progression (30%). The median duration of the response was 24 weeks (range 8–57 weeks). The progression-free survival was 15 weeks (range 3–63 weeks). No relationship between the response rate and site of metastases, ECOG performance status and age (70–75 years versus >75 years) was observed. The median survival was 41 weeks (range 2–164 weeks): 56 weeks for patients with a PR, 47 for those with SD and 32 for those who progressed. The actuarial 1-year survival was 30% (CI: 21–91%).

Of the patients evaluated, there were 11 who at the time of inclusion did not meet the criteria for assessment of palliative benefits. Therefore, this analysis was conducted on 79 patients (Table 2). Considering the performance status, 23 patients improved (29%), 39 remained stable (49%) and 17 worsened (22%). Pain score improved $\geqslant 50\%$ with no need to increase analgesia, or analgesic consumption was reduced in $\geqslant 50\%$ without worsening pain in, 29 patients (37%), remained stable in 45 (57%), and worsened in 5 (6%). Among those 18 patients whose pain score improved, the average decrease in the MPA score was 21 (range 12–40). Among the 17 patients who diminished the analgesic consumption, the average decrease was 30 mg (range 10–60). There was an improvement of anorexia in 27 (34%) patients (median VAS score 27, range 15–45), of asthenia in 13 (16%) (median VAS score 24, range 15–30) and an increase body weight greater than 5% in 9 (11%) patients (median 4.9 kg, range 3.9–5.7 kg). Overall, 31 patients (39%, 95% CI: 28–50%) had a clinical benefit (improvement of performance status without a worsening of symptoms or relief of symptoms without a worsening of the performance status). The medium time for clinical benefit was 15 weeks. A clinical benefit was observed in 11/13 (85%) patients who reached a PR and met the criteria for the assessment of palliative benefits, while amongst those who had a SD, a clinical benefit was detected in 20/41 (49%). No patient with radiological progressive disease achieved a clinical benefit.

3.3. Toxicity

In general, the treatment was well tolerated. In total, 66 patients (73%) suffered some toxicity, usually of grade 1-2. The main toxicities were gastrointestinal and haematological. 12 patients (13%) developed grade 3-4 side-effects (Table 3): 7 had nausea/vomiting (8%), 6 a transaminase increase (7%), 4 asthenia (4%), 3 diarrhoea (3%), 2 neutropenia (2%), 2 anaemia (2%) and 1 thrombocytopenia (1%). Three toxic deaths occurred (3%): A 74-year-old man, with bone and lung metastasis, with an ECOG performance status of 2, died with pancytopenia and sepsis after the first cycle. Another death occurred in a 76-year-old woman with liver metastasis and an ECOG performance status of 2, who died as a consequence of diarrhoea and sepsis 3 weeks after the second cycle. Lastly, a 77-year-old woman with peritoneal carcinomatosis and an ECOG performance status of 2 suffered intestinal obstruction with renal failure following the first cycle, leading to neutropenic sepsis and death.

The possible influence of age and gender on the occurrence of different grade 3-4 toxicities was analysed. Amongst elderly patients $\geqslant 75$ years, a greater frequency of grade 3-4 nausea/vomiting (0/51 versus 7/39; $P<0.01$), grade 3-4 hepatotoxicity (0/51 versus 6/39; $P<0.01$) and grade 3-4 diarrhoea (0/51 versus 3/39) were observed, although in this latter case the differences were not statistically significant ($P=0.09$). Regarding gender, only a tendency towards a higher frequency of grade 3-4 diarrhoea was detected in women compared with men (3/42 versus 0/48; $P=0.09$). As for the influence of renal function on the occurrence of toxicity, 8/18 patients with a creatinine clearance $\leqslant 1.08$ ml/s versus 4/72 patients with a creatinine clearance of >1.08 ml/s ($P<0.001$) were observed to develop a grade 3–4 toxicity. No relationship was found between comorbidity, as measured by the Charlson scale [22], and toxicity.

Table 2
Clinical benefit

Characteristic	Improvement	Stabilisation	Progression
	n (%)		
ECOG performance status	23 (29)	39 (49)	17 (22)
Pain	29 (37)	45 (57)	5 (6)
Anorexia	27 (34)	36 (46)	16 (20)
Asthenia	13 (16)	47 (59)	19 (24)
Weight loss	9 (11)	51 (65)	19 (24)

ECOG, Eastern Cooperative Oncology Group.

Table 3
Treatment toxicities per patient

WHO toxicity	Grade 1-2 *n* (%)	Grade 3-4 *n* (%)
Nausea/vomiting	38 (42)	7 (8)
Diarrhoea	24 (27)	3 (3)
Transaminase increase	16 (18)	6 (7)
Neutropenia	8 (9)	2 (2)
Anaemia	24 (27)	2 (2)
Thrombocytopenia	1 (1)	1 (1)
Mucositis	11 (12)	
Alopecia	9 (10)	
Asthenia	12 (13)	4 (4)
Others	9 (10)	1 (1)

WHO, World health Organization.

4. Discussion

Presently, advanced colorectal cancer is an incurable disease. For that reason, the objective of the treatment must be aimed at prolonging survival, obtaining an effective control of the symptoms and maintaining or improving quality of life. These objectives should be reached with an acceptable level of toxicity that does not deteriorate the patient's quality of life. If furthermore we deal with an elderly person, even greater caution must be used when choosing the antineoplastic treatment and it is necessary to consider other aspects that may influence the tolerance of the treatment, such as pharmacological changes that occur with age or comorbidity [24].

Although during recent years the need to include the elderly in clinical trials has been stressed, there is still very little experience in that field and therefore few data are available on the efficacy and toxicity of cytostatic agents in this population. The retrospective studies performed on patients with advanced colorectal cancer that have investigated the influence of age on the response to chemotherapy have not detected changes in the elderly [14,25]. In our series, the response rate reached with raltitrexed was 22%, which is similar to the 19–22% responses reported by other authors who used this same treatment in other age groups [17,18]. There might be more controversy regarding the possible benefits of the treatment on survival. While in the general population there are several randomised studies that suggest that chemotherapy increases survival of patients with advanced colorectal cancer [10–12], only one randomised study has been conducted with elderly patients and its results do not enable us to resolve the question. In the study mentioned, 163 elderly patients were included with various gastrointestinal tumours, of which 54% were advanced colorectal cancer, and they were randomised to receive chemotherapy with 5-FU-LV or the best supportive treatment. In the group treated with chemotherapy only a tendency towards an increase in survival was observed (7.5 versus 5.5 months), but with no statistical significance [26]. Furthermore, the data from the retrospective studies are also unclear. While in one study the survival rate in the elderly $\geqslant 70$ years treated with 5-FU-LV was observed to be significantly lower than in patients younger than 70 years (42 versus 50 weeks; $P = 0.04$) [14], no differences were detected in another study [8]. In our series, the median for survival reached 41 weeks which is similar to the survival reported in other studies performed with raltitrexed that included patients with advanced colorectal cancer belonging to different age groups [18,19].

Another aspect to consider when evaluating the benefits of chemotherapy is the alleviation of the symptoms. In our series, 39% of evaluable patients obtained a clinical benefit. This effect could be observed not only in the patients who reached a PR, but also in those patients with SD [17]. In fact, in our series, 49% of patients with SD obtained a clinical benefit.

There is a clear concern amongst oncologists that chemotherapy may do more harm than good in the elderly, especially when the aim of the treatment is palliative. In our study, we did not observe a higher toxicity with raltitrexed treatment in the elderly than the toxicity described with this drug in other age groups nor was there an increase in the proportion of toxic deaths [17,18]. In fact, the 3% of deaths attributable to treatment toxicity observed in our series does not differ from the toxic death rate reported in the studies using 5-FU-LV [14,17] and is even below the 9% indicated in a retrospective study that analysed several regimens of 5-FU-LV in the elderly [8]. Grade 3-4 toxicity was rare, with nausea and vomiting, and a transaminase increase being the most common toxicities, although less than 10% of the patients experienced these toxicities. It is worth stressing the limited incidence of myelosuppression, diarrhoea and mucositis observed in our series. Similar results have been reported from randomised trials that compared the administration of raltitrexed to that of 5-FU-LV [15,18,27]. In spite of this favourable toxicity profile of raltitrexed, special attention should be paid to renal function when this drug is used. It has been noted that 35% of patients with elevated serum creatinine values treated with this drug presented grade 3-4 diarrhoea [15]. In our series, we observed that 44% of the patients with a creatinine clearance 1.08 ml/s presented some grade 3-4 toxicity. These data are of special relevance at these ages since a seriously decreased creatinine clearance may exist with a normal serum creatinine level which could predispose to the occurrence of a serious toxicity. Although in our protocol a dose reduction was recommended for clearances between 0.42 and 1.08 mg/s, our findings lead us to recommend that raltitrexed administration is delayed in elderly patients until a creatinine clearance above 1.08 ml/s is obtained.

An additional aspect to take into account in the elderly is the patient's compliance. It is known that elderly patients are reluctant to return repeatedly to the hospital. In that sense, raltitrexed offers the advantage of its convenient administration, with a rapid infusion of 15 minutes duration repeated every 3 weeks. This dosage is simpler than other regimens. In fact, in a study which compares the patient's preferences regarding treatment with raltitrexed or other 5-FU-based regimens, it was observed that 80% of the patients expressed their preference for raltitrexed [28].

In conclusion, the results of the present study show that raltitrexed is a good therapeutic option for the palliative treatment of elderly patients with advanced colorectal cancer. Whether its combination with other

cytostatic agents may improve its efficacy without significantly increasing toxicity still remains to be defined.

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