

Chemotherapy in Elderly Patients with Metastatic Colorectal Cancer: Relations to Co-morbidities and Functional abilities

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Abstract: Introduction: We aimed to study the management of a cohort of elderly patients (≥ 65 years old) with metastatic colorectal cancer (mCRC) treated by our oncology team between April 2010 until December 2012 in relation to their comorbidities and functional abilities. **Patients and methods:** That was an observational prospective study of 43 patients with mCRC. **Results:** Thirteen patients were treated with XELOX (oxaliplatin and capecitabine) regimen. They had Cumulative Illness Rating Scale for Geriatric (CIRS-G) score of 0-3, Lawton Instrumental Activity of Daily Living (IADL) score of 8 and performance status (PS) of 1. Partial response (PR) of 61.5% and stable disease (SD) 30.8% were achieved. The median progression free survival (PFS) and overall survival (OS) durations were 10 and 16 months respectively. Ten patients had oral capecitabine. They had CIRS-G score of 0-3, IADL score of 4-8 and PS 2. Two had PR (20%) and 6 SD (60%). The median PFS and OS were 11 and 12 months respectively. Five patients were treated with FOLFIRI (Irinotecan and modified Degramont) regimen. They had CIRS-G 1-3, Lawton IADL of 5-8 and PS 1-2. Two patients had PR (40%) and 1 (20%) SD. Median PFS and OS were 9 months and 14 months respectively. Fifteen patients had ischaemic heart diseases were treated with Raltitrexed. They had CIRS-G score of 2-3, IADL score of 4-8 and PS 1-2. PR and SD rates were 35.7% each. Median PFS and OS were 7 and 10 months respectively. **Conclusion:** CIRS-G score, IADL and PS are quite helpful tools in assessing elderly patients prior to chemotherapy.

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1. Introduction:

Colorectal cancer (CRC) is the fourth most common cancer worldwide and is the second commonest cause of cancer-related mortality [1]. Colorectal cancer (CRC) is the third most common cancer in the UK, accounting for 13% of all new cases. Between 2007 and 2009, an average 72% of bowel cancer cases were diagnosed in people aged 65 years and over [3-4]. The relative survival of elderly (≥ 65 years) CRC patients is generally worse than that of younger patients due to more advanced stage at presentation and also due to the fact that they often receive suboptimal management [5]. In a study by Koroukian et al [6] co-morbidities were associated with increased likelihood of surgery-only, but not with surgery and chemotherapy. Both functional limitations and geriatric syndromes were associated with lower likelihood to undergo either surgery-only or surgery and chemotherapy [7].

Cumulative Illness Rating Scale for Geriatric (CIRS-G) [8-9] and Lawton Instrumental Activities of Daily Livings (IADL) [10] are frequently-used to assess the degree of co-morbidity and functional abilities in elderly patients. Four geriatric syndromes are of particular importance to the elderly; first weight

loss and frailty, second falls and walking problems, third dementia, delirium, decisional capacity and finally, the polypharmacy [11].

Oncologists are always, faced with the challenge of determining the optimal treatment for patients with co-morbidities or aging. In this observational study, we studied the management of a cohort of elderly patients with metastatic colorectal cancer (mCRC) in relation to their performance status, co-morbidities and functional abilities.

2. Patients and methods

This was an observational study of a cohort of patients with mCRC who were 65 years or older treated with first line palliative chemotherapy in our oncology centre between April 2010 until December 2012. Demographic data, performance status according to Eastern Cooperative Oncology Group (ECOG), degree of co-morbidities according to CIRS-G [8] and functional abilities according to Lawton IADL [10] were recorded. CIRS-G [8] was calculated according to the degree of co-morbidities involving different body organs by assigning scores as follow:

Degree of Co-morbidity	Score
• No problem	0
• Current mild problem or past significant problem	1
• Moderate disability or morbidity requiring first line therapy	2
• Severe/constant significant disability/un-controllable chronic problems	3
• Extremely severe/immediate treatment is required/end organ failure/severe impairment in function	4

A total score is then calculated with particular focus on level 3 or 4 co-morbidities.

The Lawton IADL scale [10] was calculated for 8 daily functional activities:

- Ability to use telephone
- Food preparation
- House keeping
- Laundry
- Responsibility for own medications
- Mode of transportation
- Shopping
- Ability to handle finances

A score of either 0 or 1 is assigned for each of the 8 patient's functional abilities. A summary score ranges from 0 (low function, dependent) to 8 (high function, independent).

Four different palliative chemotherapy regimens were used in the treatment of our patients. The XELOX Regimen: Oxaliplatin 130mg/m² was administered intravenously, over 2 hours on day 1 followed by oral capecitabine 1000 mg/m² twice daily for 14 days every 3 weeks. Oral Capecitabine: 1000 mg/m² twice daily for 14 days every 3 weeks. Irinotecan and modified Degramont (IrMdG) Regimen: Irinotecan 180 mg/m² intravenous (iv) infusion over 90 min followed by folinic acid 400 mg/m² iv over 2 h, then fluorouracil (5FU) 400 mg/m² iv bolus and 5FU 2400 mg/m² continuous iv infusion for 46 h every 2 weeks. Raltitrexed: 3 mg/m² intravenous over 15 minutes every 3 weeks.

Response to treatment was recorded according to the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1). SPSS statistical package version 16.0 was used in data analysis. Progression free and overall survival probabilities were assessed using the Kaplan Meir method.

3. Results

Forty three patients were included into the study. Thirteen patients received XELOX regimen. Patients in this group had 1-2 co-morbidities which were mostly chronic obstructive pulmonary disease (COPD) with CIRS-G between 0-3. All of them were independent in

their daily activities (score 8) with PS 1. Four of them had adjuvant oral capecitabine for stage Duke's C disease at initial presentation. Three patients had initially 25% dose reduction for co-morbidities and 7 patients for significant toxicities.

Ten patients were treated with oral capecitabine; all were ≥ 70 years and had a median of 2 co-morbidities mostly moderate renal impairment (GFR 30-50 ml/min) and/or diabetes mellitus. Most of them had CIRS-G score of 2, Lawton scale 5 and PS 2. In our practice, the starting dose was 1000 mg/2 twice daily for 14 days in 3 weekly cycle. Further 25% dose reduction was required in 7 patients for either co-morbidities (4 patients with moderate renal impairment) or further repeated grade 2 toxicities (3).

Five patients were treated with FOLFIRI regimen. Each of them had one co-morbidity; 3 had previous thromboembolic event (DVT/PE) and 2 rheumatoid arthritis. Four scored 1 in CIRS-G and 1 scored 3. Four scored 8 in IADL and 1 scored 5. They had previous exposure to adjuvant chemotherapy with oxaliplatin and flouropyrimidines regimens but had recurrent distant metastatic disease. Dose reduction was required in 2 patients due to toxicities (tables 1 and 2).

Raltitrexed was used in 15 patients with ischemic heart diseases (IHD) as their main co-morbidity as flouropyrimidines were avoided in those patients. Ten patients had CIRS-G of 2, five patients had CIRS-G of 3 (renal impairment and ischaemic heart disease). No patients had level 3 severity. All had PS 1-2 and acceptable independence in their daily activities with Lawton scale ranges 4-8. Three patients were exposed to capecitabine as either adjuvant chemotherapy or part of long course chemo-radiotherapy but developed angina which mandated stoppage of capecitabine. Raltitrexed was administered at a dose of 3 mg/m² every 3 weeks but further dose 25% reduction was needed in 3 patients due to mild renal impairment in 1 patient (given 4 weekly) or due to intolerable side effects (2 patients).

In the XELOX group, a median of 6 cycles (range 4-8 cycles) were administered. Partial response (PR) of 61.5% and stable disease (SD) of 30.8% were achieved. Twelve patients had second line chemotherapy with either FOLFIRI (10) or oral capecitabine (2 patients).

In the capecitabine group, a median of 7 cycles were administered (range 4-12). 2 patients had PR (20%) and 6 SD (60%). One patient had further chemotherapy with XELOX on progression.

In the FOLFIRI group, 10-12 cycles were administered for each patient (median 11). Two patients achieved PR (40%) and 1 (20%) stable disease.

In the Raltitrexed group, a median of 4 cycles (range of 1-9 cycles) were administered. Fourteen patients were assessable for response. PR and SD rates

were 35.7% each. Only 1 patient had second line irinotecan (table 2).

There were no significant relation between the response to chemotherapy and the levels of CIRS-G, number of co-morbidities or functional abilities

observed in this study. Better response rates were associated with PS of 1 and lower responses with PS 2. Higher partial response was achieved with XELOX regimen although disease stabilisation was possible as well with all other regimens.

Table 1. Relation of Chemotherapy Regimens to Patients' Characteristics

	XELOX	Capecitabine	FOLFIRI	Raltitrexed
Number of Patients	13	10	5	15
Age, N (%)				
65-<70	3 (23.1)	0	3 (60)	4 (26.7)
70 or more	10 (76.9)	10 (100)	2 (40)	11 (73.3)
Co-morbidities, N (%)				
0	1 (7.7)	2 (20)	0	0
1	10 (76.9)	4 (40)	5 (100)	12 (80)
2	2 (15.4)	4 (40)	0	3 (20)
CIRS-G, N (%)				
CIRS-G 0	1 (7.7)	2 (20)	0	0
CIRS-G 1	6 (46.2)	1 (10)	4 (80)	0
CIRS-G 2	5 (38.5)	5 (50)	0	10 (66.7)
CIRS-G 3	1 (7.7)	2 (20)	1 (20)	5 (33.3)
CIRS-G level 3 severity				
CIRS-G level 4 severity				
IADL, N (%)				
Score 4	0	2 (20)	0	2 (13.3)
Score 5	0	6 (60)	1 (20)	5 (33.3)
Score 8	13 (100)	2 (20)	4 (80)	8 (53.3)
PS, N (%)				
1	13 (100)	-	4 (80)	8 (53.3)
2	0	10 (100)	1 (20)	7 (46.7)

IADL: Independent activities of daily livings, CIRS-G: Cumulative Illness Rating Scale for Geriatrics, PS: Performance status

Figure (1) Progression Free Survival (PFS) For All Patients After First Line chemotherapy

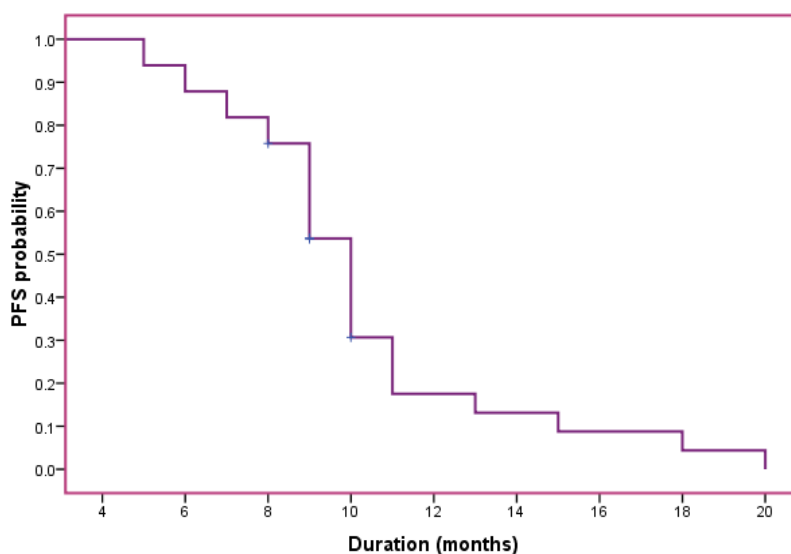
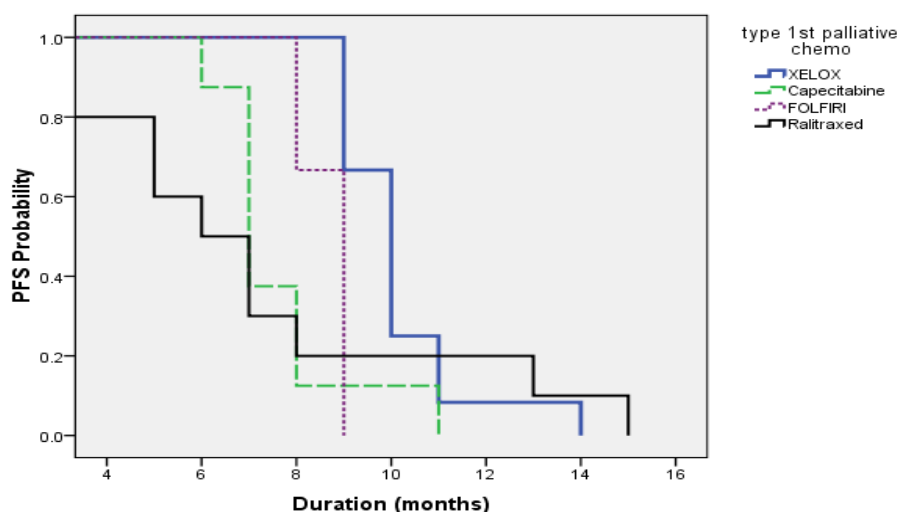


Table 2 Chemotherapy Regimens, Tumour Characteristics and Outcome

		XELOX N (%)	Capecitabine N (%)	FOLFIRI N (%)	Raltitrexed N (%)
Patients' Number (%)		13 (100)	10 (100)	5 (100)	15 (100)
Primary tumour site	Colon	10 (76.9)	5 (50)	3 (60)	10 (66.7)
	rectum	3 (23.1)	5 (50)	2 (40)	5 (33.3)
Resection of Primary tumour	Yes	5 (38.5)	2 (20)	5 (100)	7 (46.7)
	No	8 (61.5)	8 (80)	-	8 (53.3)
Adjuvant chemotherapy	Yes	4 (30.8)	2 (20)	5 (100)	1 (6.7)
	No	-	-	-	5 (33.3)
	Initially metastatic	9 (69.2)	8 (80)	-	9 (60)
Neoadjuvant CRT	Yes	1 (7.7)		2 (40)	2 (13.3)
	No	12 (92.3)	10 (100)	3 (60)	13 (86.7)
Recurrence	local	-	-	-	2 (13.3)
	distant met	4 (30.8)	2 (20)	5 (100)	4 (26.7)
	Primary met	9 (69.2)	8 (800)	-	9 (60)
SACT met/Responses	N (%)				
Dose Reduction, reason	Yes, co-morbidities	3 (23.1)	4 (40)	-	1 (6.7)
	Yes, toxicities	7 (53.8)	3 (30)	2 (40)	2 (13.3)
	No	3 (23.1)	3 (30)	3 (60)	12 (80)
chemotherapy cycles Number	Range (median)	4-8 (6)	4-12 (7)	10-12 (11)	1-9 (4)
Response	PR	8 (61.5)	2 (20)	2 (40)	5 (35.7)
	SD	4 (30.8)	6 (60)	1 (20)	5 (35.7)
	PD	1 (7.7)	2 (20)	2 (40)	4 (28.6)
	Not assessable	-	-	-	1
Median Survival (m)	PFS	10 (8-12)	8 (7-9)	9 (7-11)	7 (4-10)
	OS	16 (13-20)	11 (9-13)	13 (12-14)	10 (7-12)

CRT: chemoradiotherapy PR: partial remission, SD: Stable disease, PD: progressive disease, SACT met: systemic anticancer treatment for metastatic disease, **m**: months, N: number, PFS: progression free survival, OS: Overall survival

Figure (2) Progression Free survival In Responding patients In Relation to Chemotherapy Regimens

The median progression free survival (PFS) duration for all patients was 10 months. For the XELOX group, it was 10 months (range 8-12), for

capecitabine group 7.8 months (range 7-9), FOLFIRI 9 months (7-11) and Raltitrexed 7 months (4-10). These differences were statistically significant ($p < 0.020$, using

the Log Rank test) (figures 1 and 2). In regression analysis, response to first line palliative chemotherapy was the only significant factor associated with longer PFS (p 0.001) and that was confirmed as well by the Log Rank test.

The median survival for all patients in this study was 14 months. In XELOX patients, that was 16

months (range 13-20 months); 14 months in FOLFIRI (range 9-13); 11 months in capecitabine (9-13 months) and 10 (7-12 months) for Raltitrexed. These differences were statistically significant (p 0.007 using the log rank test) (figures 3 and 4).

Figure (3) Overall Survival Among the Studied Patients

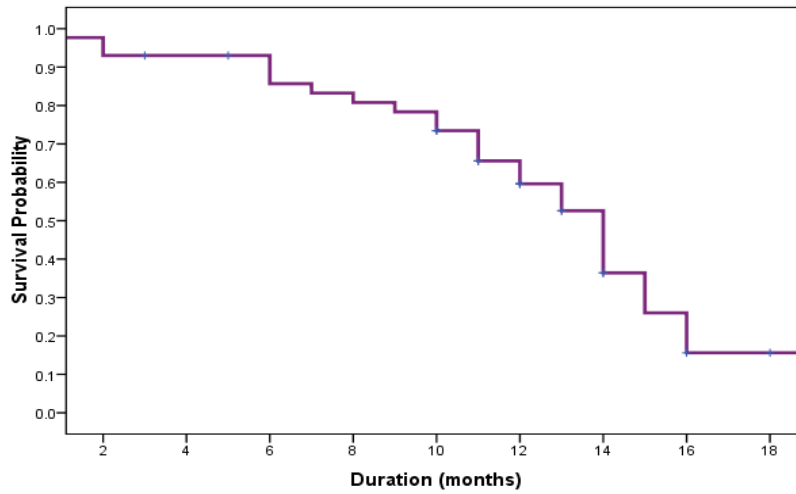
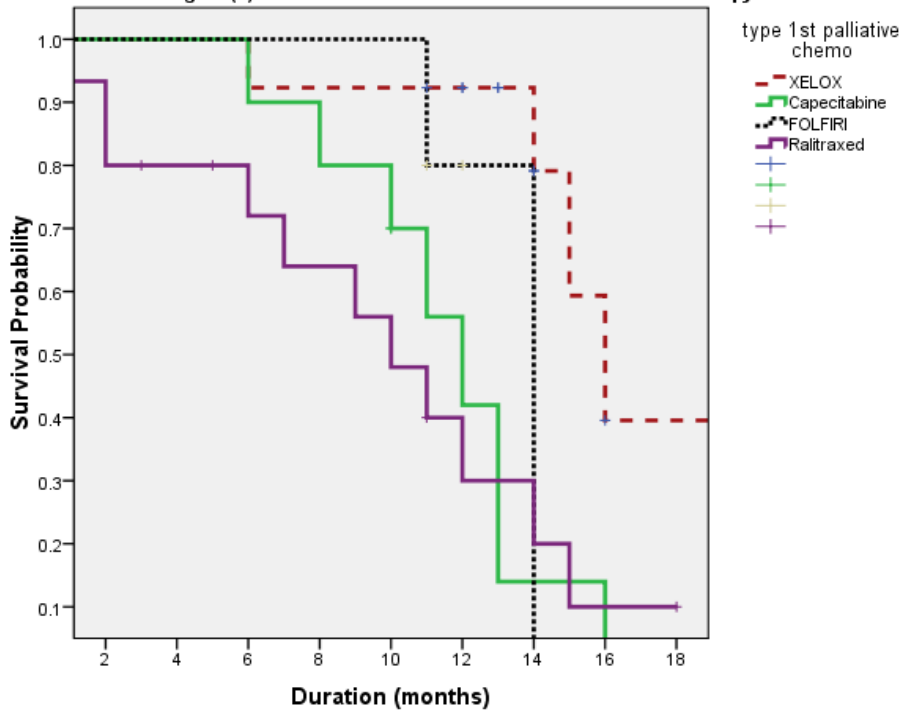


Figure (4) Survival in Relation to Different First Line Chemotherapy



In this study, the most common grade 2 toxicities with XELOX regimen were diarrhoea in 4 patients, lethargy in 2 patients, PPE in 4, neutropenia in 1 patient. With capecitabine, grade 2 toxicities included diarrhoea in 5 patients, PPE in 1. For FOLFIRI, these were diarrhoea (3 patients) and lethargy (3 patients). Raltitrexed was also associated with grade 2 diarrhoea (4 patients), lethargy (4) and anaemia in 1 patient. No grade 3 or higher toxicities were reported among the studied patients. These toxicities were more common in patients who had CIRS-G 2 or higher.

4. Discussion

Approximately 60% of all cancers and 70% of cancer mortality occur in persons aged 65 years or over. Older patients are a highly heterogeneous group, with varying levels of risk for functional or physical decline and mortality. Most authors however agree that age alone should not be used to deny chemotherapy for the elderly [12-13]. However, chemotherapy complications are more common in the older patients due to age-related physiological changes [14] and therefore, patients aged 75 or older were less likely to receive chemotherapy, even when they had few or no comorbidities [15].

In this study, patients in the XELOX group had mild co-morbidities with CIRS-G ranged between 0-3 (median 1). They were completely independent of daily activities with PS 1 despite most of them were 70 years or older. This level of good general health encouraged the use of combination chemotherapy regimens. Three patients had 25% initial dose reduction for concern about their level of co-morbidities. They did not require any further dose reduction during the course of treatment. Seven patients had similar dose reduction for recurrent grade 2 toxicities. At this dose level- partial response (PR) of 61.5% and SD 30.8% were achieved with median PFS and OS of 10 and 16 months respectively. Overall the regimen was well tolerated and effective in this patient group.

Similar findings were reported by Twelves et al [16] who compared data from older and younger patients treated with first-line XELOX at the same standard dose level. They had 96 patients in this study including 52 younger patients (<65 years of age) and 44 older patients (≥ 65). The XELOX regimen had a similar high activity in both groups, with a response rate (RR) of 58% (95% CI, 43%-71%) and 52% (95% CI, 37%-68%) in the younger and older patients, respectively. In addition, the PFS and OS were similar in both groups ($p > 0.5$ for both outcomes). The XELOX regimen also had a favourable safety profile, with no clinically relevant differences between older and younger patients. The overall incidence of adverse events (including grade 3/4), dose reductions and withdrawals because of adverse events were similar in

both groups. In the context of an aging population, XELOX provided a highly effective and tolerable first-line treatment for patients with metastatic colorectal cancer [17].

In the oral capecitabine group, patients were 70 year or older, with CIRS-G ranged between 0-3 (median 2), IADL ranged between 4-8 and PS of 2. Because of those features, single agent capecitabine was felt to be more appropriate than combination chemotherapy. The starting dose was 1000 mg/m² bd for 14 days in a 3 weekly cycle. Further 25% dose reduction was required in 7 patients for co-morbidities (moderate renal impairment) or toxicities (mostly for grade 2 diarrhoea). With this level of co-morbidity and dose levels, capecitabine was felt to be have effective tumour control in 80% of patients for a median of 8 months.

Capecitabine metabolism in the liver and tumour cells to fluorouracil (5FU) permits more prolonged cell exposure to the drug but lower plasma concentrations and, consequently, lower toxicity (hand-foot syndrome, diarrhoea, vomiting and mucositis) than 5FU. Capecitabine mimics the continuous infusion of 5FU with the advantage (or disadvantage in the elderly because of risk of dosing errors) of oral administration. Over 70% of its metabolites are excreted by the kidney, so it is contra-indicated in patients with severe renal impairment (creatinine clearance below 30 ml/min) and should be given at doses reduced to 75% to patients with moderate renal impairment (creatinine clearance 30-50 ml/min). It is still unknown whether this drug crosses the blood-brain barrier [18].

To determine the tolerability of capecitabine in patients ≥ 70 years old with advanced CRC, 51 patients, received oral capecitabine 1250 mg/m² twice daily on days 1 to 14 every 3 weeks [19]. Patients with a creatinine clearance of 30 to 50 ml/min received a dose of 950 mg/m² twice daily. The overall RR was 24% (95% CI, 15% to 41%), including 4% complete remission (CR) and 20% partial remission (PR). Disease control [CR + PR + stable disease (SD)] was achieved in 67% of patients. The median time to progression (TTP) and OS were 7 months (95% CI, 6.4 to 9.5 months) and 11 months (95% CI, 8.6 to 13.3 months), respectively which are nearly similar to our study. Capecitabine was well tolerated suggesting that it is effective and well tolerated in elderly patients with advanced CRC who are considered ineligible for combination chemotherapy.

Capecitabine has demonstrated similar efficacy and tolerability at dose of 1250 mg/m² twice daily as 5-FU in older patients being treated for colorectal cancer and breast cancer with normal renal function [18]. On the other hand, the efficacy of 1000mg/m² twice daily has been shown to be similar 1250 mg/m²

and should be considered as the starting dose for elderly patients with good renal function [19].

Five patients were treated with FOLFIRI regimen in this study. They were mostly independent in their daily activities and had CIRS-G 1 in 4 of them. Tumour control was achieved in 60% of the cases (PR of 40% and SD of 20%) with median PFS and OS durations were 9 months and 13 months respectively. Toxicities were moderate with 2 patients required dose reduction.

In a study by François et al [20], 40 elderly patients (70 or above) with metastatic CRC with a performance status of 0/1, without geriatric syndrome and without previous palliative chemotherapy, received FOLFIRI regimen in similar doses to our study and similar outcome (objective response rate was 40% and the stabilisation rate was 45%). Median progression-free survival was 8 months, and cancer specific survival was 20.2 months). Tolerance was good; grade 3/4 toxicities included diarrhoea (15%), asthenia (15%), nausea/vomiting (7.5%) and neutropenia (7.5%). One toxic death was observed due to grade 4 diarrhoea.

Raltitrexed (Tomudex) is a specific inhibitor of thymidylate synthase (TS). Raltitrexed enters cells via the reduced-folate carrier and is polyglutamated by folylpolyglutamate synthase, which increases intracellular retention and leads to prolonged TS inhibition, DNA fragmentation and cell death. The mechanism of action of raltitrexed differs from that of 5-FU and its serum terminal half life is longer (148–379 h), which allows raltitrexed to be administered with an extended dosing interval, every 3 weeks [21–22].

Raltitrexed was used in the treatment of 15 of our patients who had ischemic heart disease (IHD) and/or history of angina while been on oral capecitabine in the adjuvant setting. Fluoropyrimidine regimens were thought to be better avoided in those patients. Ten patients had CIRS-G of 2 and five had CIRS-G 3. They had PS ≤ 2 and acceptable independence in their daily activities with Lawton scale ranges 4–8.

Most patients had a dose level of 3 mg/m² but 25 % dose reduction was needed in 3 patients due to mild renal impairment (1 patient) or due to intolerable side effects (2 patients). PR and SD rates were 36% each. The median PFS was 7 months and median survival was 10 months. Raltitrexed was also associated with grade 2 diarrhoea (4 patients), lethargy (4) and anaemia in 1 patient. No grade 3 or higher toxicities were reported among the studied patients.

The efficacy of Raltitrexed as monotherapy in patients with advanced CRC has been shown in three phase III clinical studies (studies 3, 10 and 12) in which raltitrexed was compared with two standard 5-FU-based regimens (the Mayo and Machover

regimens). The 4 mg/m² dose of raltitrexed was discontinued because of unacceptable toxicity and 3mg/m² continued to be the standard dose. Objective responses with raltitrexed included CR 3.6%, PR 15.7%, with PFS 4.8 months and OS 10.1 months in study 3. In study 10, they were 2.8%, 11.5%, 3.1, 9.7 months. In study 12, they were 3.2%, 15.4%, 3.9 and 10.7months. Palliative benefits of treatment included weight gain and improvements in performance status and disease-related symptoms, and were seen in all trials, with the greatest benefits being seen in patients who achieved complete or partial remission or disease stabilization (45-70% of all patients) [23–26].

On conclusion, we feel that well controlled co-morbidities are not against offering palliative chemotherapy so long as the patient's daily functional ability is reasonably maintained with performance status of 2 or better. CIRS-G of ≥ 4 , IADL of ≤ 4 , PS of 2 are against combination chemotherapy especially if associated with features of geriatric syndromes. The fit elderly should not be denied chemotherapy treatment but initial dose reduction is advisable as complications from cytotoxic chemotherapy are more common in the older patients due to age-related physiological changes. Subsequent dose escalation may be considered if the chemotherapy regimen is well tolerated.

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