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ORIGINAL PAPER

Continuous, low-dose capecitabine for patients with recurrent colorectal cancer

Adriana Romiti · Concetta Elisa Onesti · Michela Roberto · Viola Barucca · Silverio Tomao · Chiara D'Antonio · Valeria Durante · Annalisa Milano · Rosa Falcone · Roberta Di Rocco · Riccardo Righini · Paolo Marchetti

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Abstract The aim of the study was to retrospectively assess the efficacy and safety of low-dose metronomic oral capecitabine in pretreated or frail patients with recurrent colorectal cancer. Patients with recurrent colorectal cancer and prior treatment with fluoropyrimidines, oxaliplatin, and irinotecan or unable to receive standard chemotherapy because of toxicity concerns were included. Treatment consisted of oral capecitabine 1,500 mg daily until disease progression or unacceptable toxicity. Response rates were determined according to RECIST criteria. The end points were disease control rate [(DCR) consisting of complete response, partial response (PR), and stable disease (SD)], overall survival (OS), and safety. Sixty-eight patients, median age 72.5 years, were treated. The median number of previous treatments was 2 (range 0–5). Sixty-two percent of patients had received $\geq$2 previous lines of treatment. The overall DCR was 26 %, PR in 2 (3 %) and SD in 14 (23 %). Nineteen percent of patients were progression free for at least 6 months. In an exploratory analysis, there was a significant relation of performance status with DCR (HR = 3.3; $P = 0.05$). The median OS was 8 months. DCR was associated with a longer survival (HR = 0.4; $P < 0.01$). Grade 3 toxicities included anemia (1), diarrhea (1), and hand-foot syndrome (1). There were no cases of grade 4 toxicity or treatment-related deaths. Metronomic capecitabine was moderately active and well-tolerated in pretreated or frail patients with recurrent colorectal cancer.

Keywords Capecitabine · Low-dose chemotherapy · Colorectal cancer · Metronomic chemotherapy

A. Romiti (✉) · C. E. Onesti · M. Roberto · V. Barucca · C. D'Antonio · V. Durante · A. Milano · R. Falcone · R. Di Rocco · R. Righini · P. Marchetti
Clinical and Molecular Medicine Department, Sapienza University, Sant'Andrea Hospital, Via di Grottarossa 1035, 00189 Rome, Italy
e-mail: adriana.romiti@uniroma1.it

S. Tomao
Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University, Rome, Italy

S. Tomao
Oncology Unit, ICOT, Latina, Italy

Introduction

Therapy for metastatic cancer basically consists in chemotherapy, which is used at the higher, tolerable dose to kill as many tumor cells as possible. However, this strategy, which is supported by a very high cure rate in preclinical studies, is unable to permanently control cancer growth. In fact, excluding some hematologic or germinal malignancies, after a period of regression or stabilization, the vast majority of tumors do relentlessly progress. The efficacy of conventional chemotherapy is prevented by several factors such as the heterogeneity and the genomic instability of tumor cells, the protective action exerted by the microenvironment and the suppression of anticancer immune responses [1].

It has been demonstrated that low doses of cytotoxic drugs, given at shorter intervals between consecutive doses and without interruption, prompted a sustained cytotoxic or apoptotic effect on the tumor vascular endothelial cells, leading to tumor regression [2, 3]. This particular chemotherapy, which directly or indirectly [4] targets the slowly proliferating tumor endothelial cells, has been named "Metronomic Chemotherapy" (MCT) [5]. Because of its activity on endothelial and cancer cells as well as its immunomodulatory effects, it has been properly used to treat drug-resistant cancers of different origin [6].

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Interestingly, in clinical trials, metronomic schedules have also shown a good tolerability, with a low incidence of severe adverse events [7, 8].

In the present study, we retrospectively evaluated the activity and tolerability of metronomic capecitabine (mCAP) in patients with colorectal cancer (CRC) either whose frailty had prevented the use of more active regimens or who had been instead heavily pretreated.

Patients and methods

Treatment protocol and patients assessment

This study enrolled 68 consecutive patients with colorectal cancer, treated with mCAP at our Institution. Inclusion criteria were as follows: histological diagnosis of a colorectal cancer; progressive disease at baseline; inability to receive standard chemotherapy because of toxicity concerns or failure of one or more previous chemotherapeutic lines for metastatic disease; age $\geq$18 years; performance status (ECOG) $\leq$3; life expectancy >3 months as clinically judged; adequate bone marrow, renal and liver function (leukocyte count $\geq$3,000/mm^3; platelet count $\geq$100.000 mm^3; creatinine <2.0 mg/dl; total bilirubin levels $\leq$1.5 mg/dl; and transaminase values <3 times normal values. Exclusion criteria were: brain metastases, symptomatic cardiac disease, recent history of myocardial infarction, active infections, inflammatory bowel disease, and pregnancy.

All patients orally received 1,500 mg of capecitabine within 30 min from dinner. Treatment was continually administrated without drug-free intervals until the occurrence of either disease progression or unacceptable toxicity.

Objective response was clinically evaluated every month. Imaging techniques were instead obtained approximately every 2 months. Response rate (RR) was assessed according to RECIST criteria. Disease control rate (DCR), which reflected the proportion of patients with complete response (CR), partial response (PR) and stable disease (SD), was used to assess the activity of metronomic capecitabine. Treatment toxicity was monthly assessed according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 3 (CTCAE version 3, 2006). Toxicity was also evaluated according to patients' age class (<70 vs. $\geq$70 years).

All patients provided a written informed consent, and protocol approval of the Sant'Andrea Hospital Ethics Committee was obtained (N. 1596/2013).

Statistical analysis

SPSS statistical software, version 22 (SPSS Inc. Chicago, Illinois, USA) was used. Chi-square test or Fisher's exact test was applied when appropriate for testing the association of treatment toxicity and patients' age class. A P value of 0.05 was considered as statistically significant. Logistic regression analysis was performed to model the association between DCR and clinicopathological parameters. Overall survival (OS) was calculated from the date of the first chemotherapy administration to the date of death (for any cause). The analysis of OS was calculated using the Kaplan–Meier method and compared using the log-rank test. Patients were censored at the last observation in the case that death had not occurred. Cox proportional hazards regression was performed to analyze the effect of all clinicopathological variables on OS.

Results

Sixty-eight patients with advanced CRC cancer were treated with mCAP, at our institution. All patients were assessable for safety. Sixty-two completed at least 8 weeks of therapy and were suitable for response evaluation (median duration that patients received treatment was 18 weeks; range 4–80 weeks). The baseline and demographic characteristics of patients are shown in Table 1. Most patients had a PS of 0 or 1. The median age was 72.5 years (range 30–85). The majority of patients had multiple sites of metastatic disease, with the most common disease spread to liver (66.2 %), lungs (60.3 %) and nodes (48.5). Almost all patients were heavily pretreated with a median of two previous chemotherapy regimens (range 0–5).

Tumor response

Overall, 62 patients completed two cycles and were evaluable for objective response. Two patients (3 %) achieved PR, 14 (23 %) SD and 46 patients (74 %) had progressive disease. The DCR was obtained in 26 % of the patients and was long term ($\geq$24 weeks) in 12 patients (19 %). When the correlation between DCR and each clinicopathological variable was examined using univariate analysis, only ECOG PS (HR = 3.3; 95 % CI 1–11.0 $P = 0.05$) was associated (Table 2). Upon multivariate analysis, ECOG PS ($P = 0.03$) and the administration of subsequent chemotherapy lines ($P = 0.05$) were independent predictors of DCR.

Overall survival

All 68 treated patients were assessable for OS, with a median follow-up duration of 6.5 months (range 1–68 months). At the time of analysis, there were 53 deaths. The median OS was 8 months (range 1–68 months; 95 % CI 3.7–12.3 months). Moreover, the median OS of

Table 1 Patient characteristics

Characteristic	Number	%
Total	68	100
Median age years (range)	72.5 (30–85)	
Gender: F/M	31/37	45.6/54.4
Tumor localization		
Colon	50	73.5
Rectum	18	26.5
Metastatic site[a]		
Liver	45	66.2
Lymph nodes	33	48.5
Others	52	76.5
Single	21	30.9
Multiple	47	69.1
ECOG performance status		
0	15	25.9
1	37	63.8
≥2	6	10.3
Previous chemotherapy		
0–1	26	38.2
2	30	44.1
≥3	12	17.7
5FU-Oxaliplatin	36	52.9
5FU-Irinotecan	55	80.9
Anti-VEGF	30	44.1
Anti-EGFR	29	42.6

[a] A patient may have more than one metastatic site

responding patients was 23 months (range 4–68; 95 % CI 6.6–39.4), whereas the median OS of non-responders was 6 months (range 1–65; 95 % CI 5.1–7.0) ($P < 0.01$, log-rank test) (Fig. 1). At univariate analysis, OS was affected by the administration of subsequent chemotherapy lines ($P < 0.001$; HR = 0.2, 95 % CI 0.1–0.4) and DCR ($P < 0.01$; HR = 0.4, 95 % CI 0.2–0.8) (Table 2). At multivariate regression analysis, both these parameters were found to be independent predictors of OS.

Safety

One patient, who had a history of atherosclerosis and cardiovascular disease, discontinued the treatment due to toxicity. He was diagnosed with a "non-ST-elevation myocardial infarction" after 6 weeks on study. Symptoms disappeared after angioplasty and stenting. Overall, the incidence of hematologic and non-hematologic toxicity was low and grade 3 toxicity was rarely reported (Table 3). According to age classes (<70 vs. ≥70 years), there was no statistically significant difference in the percentage of different toxicities (Table 4).

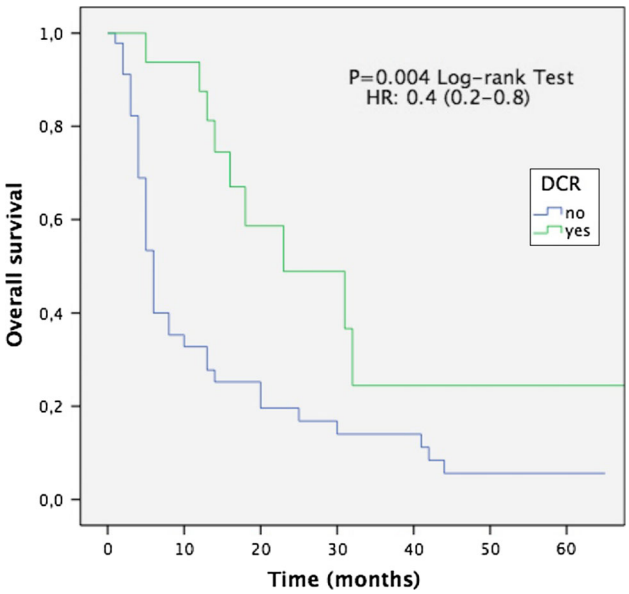

Fig. 1 Overall survival for the patient population by disease control rate (DCR)

Discussion

This study dealt with the use of mCAP in pretreated or frail CRC patients. The choice of adopting a metronomic schedule, in chemotherapy-resistant cancer patients, was driven by the accumulated evidences reporting MCT as a form of multitarget cancer therapy, rather than an exclusive antiangiogenic therapy [6]. Indeed, preclinical and clinical studies have demonstrated that MCT prompts significant immunomodulatory effects, such as the depletion of Tregs within the tumor microenvironment [9, 10]. Moreover, a number of additional mechanisms have also emerged, including the reduction of cancer cell stemness [11] or the selective inhibition of HIF-1α [12]. A recent study demonstrated the antitumor effect of mCAP on colon cancer cells both in vitro and in vivo and indicated that the inhibition of tumor proliferation may be correlated with antiangiogenesis. [13]. To our knowledge, only few studies have reported results about metronomic schedules of oral fluoropyrimidines in colorectal cancer [8, 14, 15]. In these studies, metronomic fluoropyrimidines were variously associated with other antiproliferative [8, 15] and/or anti-inflammatory drugs [8, 14], determining clinical benefit in up to 50 % of the patients.

We selected DCR as end point because it was shown to be superior to RR in predicting survival [16]. We reported a DCR of 26 % in heavily pretreated colorectal cancer patients using, continuative low doses of capecitabine. Our results were consistent with the kind of the included patients and were in keeping with those of a recent study reporting none objective response and 38 % SD in a small

Table 2 Exploratory analysis of effects of prognostic factors on clinical outcome

Relative risk (confidence interval)	Disease control rate		Overall survival	
Factor	Univariate	Multivariate	Univariate	Multivariate
Gender				
Male versus female	0.8 (0.3–2.6)	0.9 (0.2–3.8)	1.2 (0.7–2.1)	1.2 (0.7–2.2)
Age				
<70 versus ≥70	0.5 (0.1–1.6)	0.5 (0.1–2.0)	0.8 (0.5–1.5)	1.4 (0.8–2.8)
ECOG PS				
0 versus ≥1	3.3 (1–11.0)	5.0 (1.1–21.9)	0.6 (0.3–1.2)	0.8 (0.4–1.6)
Subsequent CTs				
≥1 versus Nihil	3.1 (0.9–10.3)	4.4 (1–19.9)	0.2 (0.1–0.4)	0.2 (0.1–0.5)
Tumor site				
Colon versus rectum	0.8 (0.2–2.7)	1.4 (0.3–6.8)	0.8 (0.4–1.4)	0.7 (0.3–1.3)
Liver involvement				
Yes versus no	0.6 (0.2–1.9)	0.8 (0.2–3.7)	1.5 (0.8–2.7)	1.3 (0.6–2.8)
Nodes involvement				
Yes versus no	1.1 (0.3–3.4)	1.7 (0.4–6.9)	2.1 (1.2–3.7)	1.1 (0.5–2.1)
Other organ involvement				
Yes versus no	1.2 (0.3–5.0)	1.9 (0.3–12.8)	1.1 (0.6–2.2)	0.9 (0.4–2.2)
Disease control rate				
Yes versus no			0.4 (0.2–0.8)	0.3 (0.1–0.7)

Subsequent CTs = other lines of chemotherapy administered after metronomic capecitabine

group of patients with lower gastrointestinal tract tumors [17]. Interestingly, our study showed that DCR was related to the ECOG PS and the administration of successive chemotherapy. Although this benefit was modest, concerning only a quarter of the subjects, it was, however, related to a survival advantage.

A favorable toxicity profile of mCAP with a really low incidence of severe toxicity (<10 % of the cases) and without any grade 4 adverse event was a relevant finding of our study. Moreover, we observed a comparable incidence of adverse events between older (more than 70 years old) and younger patients suggesting mCAP as a suitable treatment for elderly patients. Our data are consistent with the bulk of previous experiences showing that metronomic schedules are generally well-tolerated with a low occurrence of severe toxicity [7, 8, 18–20]. Interestingly, a relationship between the incidence of hematologic toxicity and some gene polymorphisms in patients treated with standard or even low dose of capecitabine has been recently reported, offering the opportunity of a better patients' selection [21, 22].

Ultimately, we wonder whether the licit expectation of being further treated after the failure of standard therapies should be considered if the patients maintained a good ECOG PS.

We imagine that the answer could be "yes" in case the following conditions were fulfilled: (a) the selected salvage therapy was tolerated, with a good toxicity profile; (b) the disease symptoms were at least partially controlled; (c) the disease progression was delayed in a considerable number of patients; and (d) the cost of the therapy was financially sustainable.

In conclusion, our study supports a possible role of mCAP as salvage chemotherapy for heavily pretreated or frail CRC patients holding a good PS. Metronomic

Table 3 Hematologic and non-hematologic adverse events

	Grade (% of patients)			
	I	II	III	All grades
Neutropenia	1.5	–	–	1.5
Anemia	8.8	1.5	1.5	11.8
Thrombocytopenia	1.5	2.9	–	4.4
Nausea-vomiting	2.9	5.9	–	8.8
Diarrhea	5.9	2.9	1.5	10.3
Hand-foot syndrome	5.9	1.5	2.9	10.3

Table 4 Toxicity according to age class

G1–3 toxicity	All (N.68)	<70 years (N.30)	≥70 years (N.38)	*P* value
Hematologic	12 (17.6)	4 (13.3)	8 (21.1)	0.41
Gastrointestinal	12 (17.6)	5 (16.7)	7 (18.4)	0.85
Hand-foot syndrome	7 (10.3)	3 (10.0)	4 (10.5)	0.94

capecitabine could provide a way to go on treating while at the same time monitoring toxicity. However, further prospective studies are urged to confirm these preliminary results and possibly to test in such patients combinations of mCAP with other cytotoxic and/or target molecules.

Conflict of interest None.

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