Cancer Chemother Pharmacol (2009) 64:189–193
DOI 10.1007/s00280-009-0930-z

SHORT COMMUNICATION

To widen the setting of cancer patients who could benefit from metronomic capecitabine

Margherita Nannini · Elisabetta Nobili · Roberto Di Cicilia · Giovanni Brandi · Alessandra Maleddu · Maria A. Pantaleo · Guido Biasco

Received: 1 December 2008 / Accepted: 5 January 2009 / Published online: 17 January 2009
© Springer-Verlag 2009

Abstract
Purpose We investigated the efficacy and toxicity of metronomic capecitabine administered at a fixed dose of 1,000 mg daily in three elderly or poor performance status patients with advanced colorectal cancer (CRC) and gastric cancer.
Methods In this study a pretreated advanced CRC patient (patient 1), a not previously treated advanced gastric cancer patient (patient 2), and a not previously treated advanced rectal cancer patient (patient 3) were given metronomic capecitabine administered at a fixed dose of 1,000 mg daily (day 1–28 continuously). The efficacy was evaluated every 3 months by instrumental evaluation and the treatment was continued until progression of disease or toxicity.
Results A stable disease was observed in all three patients. The duration of treatment was above 3 months and no major toxicities occurred.
Conclusions Our results indicate that metronomic capecitabine may be considered a safe and valid treatment option for advanced CRC and gastric cancer patients, both after failure of previous lines of chemotherapy or in front-line when standard chemotherapy is contraindicated, especially when the aim of medical treatment is to achieve disease control and to arrest tumour growth without affecting the patient's quality of life. Nevertheless, further clinical studies, as well as a greater clinical experience are required in order to better define the role of this strategy in medical oncology.

Keywords Capecitabine · Metronomic · Colorectal cancer · Gastric cancer · Angiogenesis

M. Nannini (✉) · E. Nobili · R. Di Cicilia · G. Brandi · A. Maleddu · M. A. Pantaleo · G. Biasco
Department of Hematology and Oncology Sciences "L. A. Seragnoli", Sant'Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy
e-mail: maggie.nannini@gmail.com

G. Biasco
Interdepartmental Centre for Cancer Research "G. Prodi", University of Bologna, Bologna, Italy

Introduction

Capecitabine is an oral fluoropyrimidine carbamate that is selectively converted to the active 5-fluorouracil (5-FU) in tumour cells by thymidine phosphorylase (TP) [1].

Currently, it is approved as a single agent for the adjuvant treatment of stage III colorectal cancer (CRC), for the first-line treatment of metastatic CRC, as an alternative to intravenous 5-FU/leucovorin and for the treatment of metastatic breast cancer patients after the prior failure of both anthracycline and taxane-based chemotherapy or when anthracycline maximum tolerated dose has been reached [2–6]. Furthermore, capecitabine has been shown to be active as a single agent for the treatment of other gastrointestinal tract tumours such as advanced gastric and pancreatic cancer [7, 8].

The standard administration schedule of capecitabine, when used as single agent, is 2,500 mg/m^2 for 14 days every 21 days.

Metronomic chemotherapy is defined as daily low-dose administration of a cytotoxic drug without treatment interruptions, characterised by a good tolerability profile and a likely antiangiogenic effect [9].

In the past years metronomic capecitabine at different daily doses has been investigated both in association with other drugs or as a single agent for the treatment of several

types of advanced tumours, showing to be more active in gastrointestinal tract cancers and breast cancer [10–14]. Nevertheless, many questions are still unsolved, such as the right setting of patients that could benefit from metronomic capecitabine and its correct daily dosage.

Despite that a standardised schedule of metronomic capecitabine does not still exist, we chose to administer 1,000 mg daily because it has been shown that this very low dose, which is nearly 1/5 of the normal dose, does not compromise the antitumour effect of the drug [10].

In this report we present our clinical experience on metronomic capecitabine administered at a fixed dose of 1,000 mg daily (day 1–28 continuously) in advanced CRC and gastric cancer patients.

Case reports

Patient 1

In June 2002 a 74-year-old female underwent an urgent anterior rectal resection due to a subocclusive stage II sigmoido-rectal adenocarcinoma. She received 5-FU/leucovorin (Mayo Clinic scheme) as adjuvant therapy, but discontinued treatment due to severe haematological and skin toxicity.

After two disease-free years, she developed pelvic relapse: she underwent surgical radical excision and then received six cycles of 5-FU/leucovorin and irinotecan (FOLFIRI regimen).

In October 2005 an abdominal CT scan showed a further unresectable pelvic relapse (Fig. 1a), which was treated with radiotherapy and chemotherapy (FOLFOX regimen), but she discontinued medical treatment early on due to a severe allergic reaction and entered in a clinical and instrumental follow-up.

In February 2007 she developed a bone recurrence and in accordance with her age and performance status we decided to treat her with metronomic capecitabine at the dose of 1,000 mg daily in association with zoledronic acid. Tumour response evaluation was assessed with a CT scan every 3 months. From May 2007 to August 2008 she received 15 cycles of chemotherapy for a total of consecutive 420 days with good tolerance and without dose reduction, obtaining a durable stable disease (Fig. 1b). In September 2008 she was admitted to hospital for a sepsis and interrupted treatment for 1 month. The subsequent CT-scan evaluation after treatment-off period showed a dimensional progression of the pelvic relapse (Fig. 1c). Therefore she now continues to receive metronomic capecitabine for other three cycles.

Patient 2

In August 2005 an 81-year-old female underwent subtotal gastrectomy due to a stage II adenocarcinoma. In October 2007 during follow-up an abdominal contrast-enhancement ultrasound (CEUS) examination two hypoechoic lesions in the VI and II hepatic segments were discovered. Because the patient was previously subjected to right quadrantectomy due to a localised ductal carcinoma, a liver biopsy was performed to define the histological nature of these lesions and it confirmed their gastrointestinal origin.

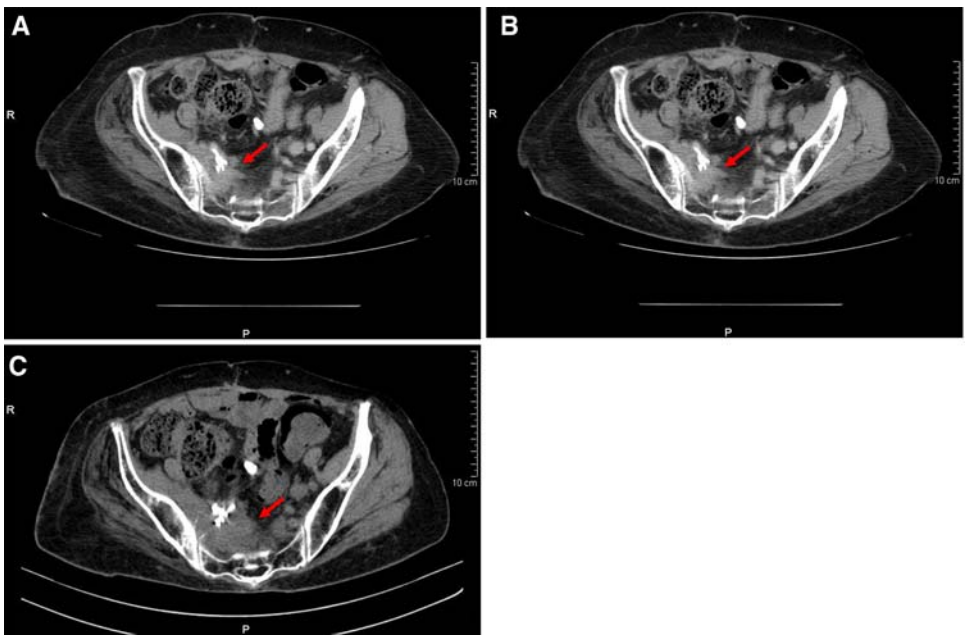

Fig. 1 Imaging studies on patient 1. **a** Pre-treatment CT-scan showing an unresectable pelvic relapse inseparable from iliac vessels with irregular profiles without bone clival plane (4 cm of diameter). **b** Post-treatment CT-scan evaluation after 15 months of metronomic capecitabine showing a dimensional stability of pelvic relapse. **c** CT-scan evaluation after 1 month of treatment period showing a dimensional progression of pelvic relapse (8 cm in diameter)

Therefore due to the advanced age and her cardiovascular comorbidity, we decided to begin a systemic treatment based on metronomic capecitabine at the dose of 1,000 mg daily. Tumour response evaluation was assessed with a thorax HR-CT scan and abdominal CEUS every 3 months, because she was allergic to iodated contrast medium. From January to August 2008 she received six cycles of chemotherapy for a total of 168 consecutive days without any adverse effect, except for a grade 1 hand-foot syndrome (HFS) completely solved with 1 week treatment interruption. The instrumental evaluation after 3 and 6 months of treatment showed a dimensional stability of hepatic lesions; therefore, she received the same treatment for an additional three cycles, for a total of consecutive 252 days with a disease stabilisation for more than 6 months.

Patient 3

In April 2005 a 78-year-old female affected by a mild vascular dementia underwent anterior rectal resection due to a stage III rectal adenocarcinoma and subsequently was treated with adjuvant radio- chemotherapy (5-FU/leucovorin plus oxaliplatin—FOLFOX regimen) until January 2006. The clinic and instrumental follow-up was negative until November 2007, when an increase of carcinoembryonic antigen (CEA) was found (14.5 ng/mL). A CT scan evaluation was negative, but according to the progressive increment of tumour marker (26.4 ng/mL) an ^{18}FDG CT-PET was performed. A pelvic pre-rectal ipermetabolic area and a focal ipermetabolic lesion in correspondence to X left rib were found. Metronomic capecitabine at the dose of 1,000 mg daily as first-line therapy was chosen in accordance with her age, the cognitive impairment, the performance status of the patient, and tumour response; evaluation was assessed with an ^{18}FDG CT-PET every 3 months. The first 3-month post-treatments ^{18}FDG CT-PET showed a complete metabolic response of all known lesions, associated with a decrease of tumour marker (CEA = 12.9 ng/mL) and an improvement of general clinical conditions. Any side effect during treatment was experienced. Therefore, the patient received the same treatment for another three cycles, for a total of consecutive 168 days and the subsequent ^{18}FDG CT-PET confirmed the normalisation of FDG uptake, associated with a stability of sieric CEA level (13.1 ng/mL).

Discussion

Metronomic chemotherapy, defined as daily low-dose administration of a cytotoxic drug without treatment interruptions, represents an interesting topic in medical oncology [15]. In fact, it not only allows to simplify the administration schedule but also to minimise the acute toxicity of cytotoxic drugs, prolonging the comprehensive duration of treatment. Moreover, the administration in small doses for a prolonged period seems to optimise the antiangiogenic effects of chemotherapy, interfering with tumour blood vessel development that occurs during the drug-free interval [16].

Since 2002, when Colleoni et al. [17–20] published the first results on continuous low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer, several studies on this treatment approach with different drugs in other tumour types have been reported. The clinical evidence confirmed low toxicity, low cost and ease of administration of metronomic chemotherapy underlining that its efficacy in cancer treatment can be significantly increased when administered in association with other antiangiogenic agents such as cyclooxygenase-2 (COX-2) inhibitors and bevacizumab.

Capecitabine, an oral pro-drug of 5-FU active both as single agent or in combination for the treatment of advanced breast cancer and different gastro-intestinal tract tumours, has also been investigated in continuous dosing schedules, as a single agent as well as in multidrug combinations [10–14] (Table 1). Lokich et al. [11] reported a retrospective analysis on 50 patients affected by different kinds of tumours and continuously treated with a fixed dose of capecitabine (1,500 or 2,000 mg/day) as a single agent or in combination with radio- and chemotherapy, observing an anti-tumour activity, especially in metastatic colon cancer subgroup. Steinbild et al. [10] in a phase II study evaluated safety and efficacy of the combination of continuous capecitabine 1,000 mg/day and celecoxib in the treatment of advanced cancer patients, monitoring the anti-angiogenic effect by dynamic contrast-enhancement magnetic resonance imaging (DCE-MRI). Nearly 30% of all patients, especially those with slow growth renal cell cancer and gastro-intestinal tract tumours, had stable disease after 3 months of therapy [10]. Metronomic capecitabine 500 mg thrice daily in combination with cyclophosphamide and bevacizumab has been shown to be minimally toxic and effective in advanced breast cancer, achieving 46% of partial response and 41% of stable disease [12]. Metronomic capecitabine in combination with preoperative pelvic irradiation in 32 rectal carcinoma patients has been shown to affect levels of circulating pro-angiogenic and anti-angiogenic factors, such as sieric VEGF and PDGF-BB, reflecting its likely antiangiogenic effect [13]. Finally Petrioli et al. [14] investigated the safety profile of continuous capecitabine at the fixed dose of 2,000 mg daily in elderly patients with metastatic CRC and gastric cancer. Besides the good toxicity profile, metronomic capecitabine produced a response rate of 22.2%, a median time to progression (TTP) of 4.4 months and a median survival of

Table 1 Studies on metronomic capecitabine as single agent or in combination regimen

Author	Year	Disease	Setting	No. pts	Type of regimen	Dose	Ref
Lokich	2004	Several types of cancer (colon cancer, genitourinary tumours, pancreatic cancer, breast cancer oesophagus cancer, tumour of unknown origin)	Advanced	58	Single agent (19) or +other agents or radiotherapy (31)	1,500 mg/day or 2,000 mg/day	[11]
Steinbild	2007	Several types of cancer (colorectal cancer, renal cell cancer, gallbladder cancer, cholangiocellular carcinoma, pancreatic cancer, other solid tumours)	Advanced	37	+Celecoxib	1,000 mg/day	[10]
Dellapasqua	2008	Breast cancer	Advanced	46	+Cyclophosphamide and bevacizumab	1,500 mg/day	[12]
Loven	2008	Rectal cancer	Neoadjuvant	32	+Preoperative pelvic irradiation	825 mg/mq twice daily	[13]
Petrioli	2008	Colorectal cancer, gastric cancer	Advanced	34	Single agent	2,000 mg/day	[14]

Table 2 Patients characteristics, treatment duration and side effects

Patient	Age	Primary tumour	Previous treatments	Treatment duration (days/no. cycles)	Side effects
1	74	Sigmoido-rectal cancer	Yes	420 (15)	Any
2	81	Gastric cancer	No	252 (9)	HFS (grade 1)
3	78	Rectal cancer	No	168 (6)	Any

9.5 months in the subgroup of metastatic CRC patients [14].

According to our clinical experience, metronomic capecitabine administered at a fixed dose of 1,000 mg daily may represent a valid treatment option for heavily treated advanced CRC and gastric cancer patients or those ones that cannot receive infusional therapies due to age and comorbidities, achieving a long disease control, ranging from 6 to 15 months, with low toxicity (Table 2).

Our report raises some considerations on metronomic capecitabine that may be a useful starting point for future larger clinical studies.

First of all, it is necessary to define which patients are most likely to benefit from metronomic capecitabine and in which clinical setting, on the basis of disease and patient-related characteristics, such as tumour type, age and comorbidity. Our clinical experience, supported by the results reported in literature up to now, may suggest that metronomic capecitabine seems to be more active in gastro-intestinal tract tumours, such as CRC and gastric cancer. In consideration to its low toxicity profile, elderly patients or patients with comorbidities may be candidates for a first-line metronomic approach when infusional therapies are contraindicated. Furthermore, it is likely that the anti-angiogenic mechanism of action of metronomic capecitabine may allow achieving a stabilisation of disease rather than a tumour response, expected of conventional chemotherapy administered at more toxic maximum tolerated doses. For this reason a metronomic approach may be indicated also for those heavily pre-treated patients resistant to other stronger regimens, in order to slow tumour growth down and achieve a stable disease as long as possible maintaining a good quality of life.

Second, until now, no one standardised dosage of metronomic capecitabine exists yet: in fact the daily doses of drugs reported in literature differ from each other ranging from 1,000 mg to 2,000 mg/day. In our clinical experience 1,000 mg/day was well tolerated and allowed to achieve a prolonged stable disease. Further clinical studies are required to define what the best fixed doses of metronomic capecitabine are on the basis of both safety and tumour activity.

Finally, it could be interesting to evaluate the integration of metronomic capecitabine with other agents or treatment modality, in order to better exploit its therapeutic potentialities and extend its clinical indications.

In conclusion, metronomic capecitabine may be considered a safe and valid treatment option for advanced CRC and gastric cancer patients, both after failure of previous lines of chemotherapy or in front-line when standard chemotherapy is contraindicated, especially when the aim of medical treatment is to achieve disease control and to arrest tumour growth without affecting the patient's quality of life. Metronomic capecitabine may become an interesting therapeutic strategy aimed at slowing down the natural history of advanced cancers; therefore, further clinical studies as well as a greater clinical experience are required in order to better define the role of this strategy in medical oncology.

References

1. Miwa M, Ura M, Nishida M et al (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
2. Twelves C, Wong A, Nowacki MP et al (2005) Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 352:2696–2704
3. Hoff PM, Ansari R, Batist G et al (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 19:2282–2292
4. Van Cutsem E, Hoff PM, Harper P et al (2004) Oral capecitabine vs intravenous 5-flourouracil and leucovorin: integrated efficacy data and novel analyses from two large, radomised, phase III trials. Br J Cancer 90:1190–1197
5. Reichardt P, Von Minckwitz G, Thuss-Patience PC et al (2003) Multicenter phase II study of oral capecitabine (Xeloda) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. Ann Oncol 14:1227–1233
6. Fumoleau P, Largillier R, Clippe C et al (2004) Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 40:536–542
7. Hong YS, Song SY, Lee SI et al (2004) A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. Ann Oncol 15:1344–1347
8. Boeck S, Wilkowski R, Bruns CJ et al (2007) Oral capecitabine in gemcitabine-pretreated patients with advanced pancreatic cancer. Oncology 73:221–227
9. Kerbel RS, Kamen BA (2004) The anti-angiogenic basis of metronomic chemotherapy. Nat Rev Cancer 4:423–436
10. Steinbild S, Arends J, Medinger M et al (2007) Metronomic antiangiogenic therapy with capecitabine and celecoxib in advanced tumor patients—results of a phase II study. Onkologie 30:629–635
11. Lokich J (2004) Capecitabine: fixed daily dose and continuous (noncyclic) dosing schedule. Cancer Invest 22:713–717
12. Dellapasqua S, Bertolini F, Bagnardi V et al (2008) Metronomic cyclophosphamide and capecitabine combined with bevacizumab in advanced breast cancer. J Clin Oncol 26:4899–4905
13. Loven D, Be'ery E, Yerushalmi R et al (2008) Daily low-dose/continuous capecitabine combined with neo-adjuvant irradiation reduces VEGF and PDGF-BB levels in rectal carcinoma patients. Acta Oncol 47:104–109
14. Petrioli R, Pascucci A, Francini E, Marsili S, Fiaschi AI, Civitelli S, Tanzini G, Battistelli S, Lorenzi M, Roviello F, Francini G, Multidisciplinary Oncology Group on Gastrointestinal Tumors (2008) Continuous oral capecitabine at fixed dose in patients older than 75 years with metastatic colorectal and gastric cancer: a study of the Multidisciplinary Oncology Group on Gastrointestinal Tumors. Anticancer Drugs 19:91–96
15. Emmenegger U, Kerbel RS (2007) Five years of clinical experience with metronomic chemotherapy: achievements and perspectives. Onkologie 30:606–608
16. Bocci G, Nicolaou KC, Kerbel RS (2002) Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective antiangiogenic window for various chemotherapeutic drugs. Cancer Res 62:6938–6943
17. Colleoni M, Rocca A, Sandri MT et al (2002) Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. Ann Oncol 13:73–80
18. Lord R, Nair S, Schache A et al (2007) Low dose metronomic oral cyclophosphamide for hormone resistant prostate cancer: a phase II study. J Urol 177:2136–2140
19. Garcia AA, Hirte H, Fleming G et al (2008) Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 26:76–82
20. Krzyzanowska MK, Tannock IF, Lockwood G et al (2007) A phase II trial of continuous low-dose oral cyclophosphamide and celecoxib in patients with renal cell carcinoma. Cancer Chemother Pharmacol 60:135–141