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

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The aim of this study was to investigate the safety profile of continuous oral capecitabine at fixed dose in patients older than 75 years, having metastatic colorectal and gastric cancer. Capecitabine was administered at a fixed dose of 2000 mg daily without interruptions. Thirty-four patients were considered evaluable for toxicity and efficacy. The median age was 81 years (range 76–85). The median duration of treatment was 113 days (range 24–238 days). No grade 4 toxicity was observed. One patient had grade 3 nausea and vomiting, and one had grade 3 diarrhea. Partial responses were observed in six patients with colorectal cancer, and in one patient with gastric cancer. This study suggests that continuous oral capecitabine at a fixed daily dose of 2000 mg is well tolerated, and that it allows for the simplification and ease of dosing in elderly patients with metastatic colorectal and gastric cancer. *Anti-Cancer Drugs* 19:91–96 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Capecitabine is an oral fluoropyrimidine, which generates 5-fluorouracil (5-FU) preferentially in tumor tissue via a three-step enzymatic conversion [1]. The activity of this oral agent was at least equivalent to the Mayo Clinic 5-FU/leucovorin, regimen both in the treatment of metastatic colorectal cancer (CRC) and as adjuvant treatment [2,3]. The drug is also largely used in patients with advanced and metastatic breast cancer, both as a single agent and in combination with other chemotherapeutic agents, most often a taxane [4,5]. In addition, capecitabine monotherapy proved to be active and well tolerated as first-line therapy in patients with other solid tumors such as advanced and/or metastatic gastric cancer [6,7].

The conventional administration schedule of capecitabine is 2500 mg/m^2 for 14 days every 21 days. This 3-week regimen has been used as a platform for combination therapy with other agents such as irinotecan, oxaliplatin and bevacizumab [8–10].

Although toxicity from capecitabine is generally acceptable and manageable, the large phase III trials, using the conventional schedule, demonstrated grade 3, hand–foot syndrome (HFS) in 17.1% and grade 3–4 diarrhea in 13.1% of patients, with the need for dose adjustment or even discontinuation of drug in a substantial proportion of patients [2,11,12]. The antitumor activity, tolerability, convenience and comfort of an oral treatment make capecitabine ideal for use in elderly patients, for whom a dose of 2000 mg/m^2 on days 1–14 every 21 days has been recommended in consideration of the deterioration of renal function in the oldest population [12].

Capecitabine is available in either 500- or 150-mg tablet sizes. Consequently, dosing by body surface area (BSA) might be impractical, and the dose is frequently rounded off to a convenient number of tablets. A specific fixed dose of capecitabine administered daily without interruptions might be useful in ensuring patient compliance and ease of administration in elderly patients, and perhaps in reducing overall toxicity. In this setting, a retrospective analysis of 50 patients with various solid tumors, with ages ranging from 37 to 78 years, showed that capecitabine administered as a continuous daily fixed dose (1500 or 2000 mg) had a low toxicity profile, with therapeutic effect even at low doses [13]. An earlier experience with continuous administration of capecitabine suggested a dose of 1331 mg/m^2/day for further studies, which corresponds to 2130–2400 mg every day for BSAs between 1.6 and 1.8 m^2 [14]. Therefore, a fixed dose of 2000 mg of capecitabine daily was considered to

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be appropriate for this study. We investigated the safety profile of continuous oral capecitabine at a fixed dose in patients above 75 years with metastatic colorectal and gastric cancer, who were considered ineligible for combination chemotherapy.

Patients and methods

The study enrolled patients with histologically proven colorectal or gastric adenocarcinoma with assessable or measurable lesions, who had not previously received chemotherapy for metastatic disease. Patients who had been treated with adjuvant 5-FU-based or capecitabine-based chemotherapy were eligible, provided they had remained disease-free for at least 6 months after the completion of the adjuvant therapy. The other eligibility criteria included an age of 76–85 years; Eastern Cooperative Oncology Group performance status of 0–2; a life expectancy of at least 3 months; adequate hematological parameters (an absolute neutrophil count of $\geq 1.5 \times 10^9$/l, hemoglobin ≥ 9.0 g/dl and a platelet count of $\geq 100 \times 10^9$/l); creatinine less than 1.6 mg/dl; total bilirubin levels < 1.25 times the upper normal limit; aspartate and alanine aminotransferase < 3.0 times the upper normal limit and the absence of a second primary tumor other than nonmelanoma skin cancer or in-situ cervical carcinoma. Patients with severe cardiac dysfunction, chronic diarrhea or uncontrolled sites of infection were excluded from the study. The measurement of the creatinine clearance was estimated using the Cockroft and Gault equation: patients with creatinine clearance < 30 ml/min were excluded from the study [15]. At study entry, a specific geriatric assessment tool was adopted, and patients were conventionally classified into three categories of fit, vulnerable and frail [16]. Patients were classified as frail if they were dependent for activities of daily living (ADLs), if they had three or more severe comorbidities, one or more geriatric syndrome or were above 85 years. Patients without relevant comorbidities who were fully independent were classified as fit; patients with only one or two significant comorbid conditions or with only instrumental ADLs, but not ADLs deficit, were classified as vulnerable. Patients classified as vulnerable or frail were considered unsuitable for combination chemotherapy and were included in the study. Elderly fit patients who refused combination chemotherapy were also included.

The study was approved by the local Ethics and Scientific Committee, and all of the patients gave their written informed consent.

Patient evaluation

The pretreatment evaluation, performed in the 2 weeks preceding the study entry, included a detailed history and physical examination, a complete blood cell count with differential and platelets, whole blood chemistry, the determination of serum carcinoembryonic antigen levels and computed tomography scans and/or magnetic resonance imaging (MRI) of the chest and abdomen. During treatment, a complete blood cell count with differential and platelets and other routine biochemical tests were performed every 4 weeks.

Treatment

Capecitabine was administered orally at a fixed dose of 2000 mg daily without interruptions. Capecitabine doses were given approximately 12 h apart, 30 min after meals. Treatment with capecitabine was continued until progression of disease, unmanageable toxic effects or withdrawal of consent.

In the analysis, the fixed dose was retrospectively converted to dose/m^2, which was based on patients' heights and weights, to enable a comparison with capecitabine doses reported in other trials.

Toxicity and dose modifications

Toxicity was assessed using the Common Toxicity Criteria of the National Cancer Institute, version 2.0. Treatment was continued at the same dose in case of grade 1 toxic effects, whereas it was interrupted for grade 2 or 3 toxicity until the event had resolved to grade 0 or 1; the capecitabine dose was then reduced to 1500 mg as a fixed daily dose. Treatment was discontinued in the case of grade 4 toxic effects or if a given event occurred at grade 2 or 3, despite dose reduction.

Response criteria

Treatment response was evaluated by means of computed tomography scan and/or MRI every 2 months or sooner if clinically indicated. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors [17]. The time to progression (TTP) was the interval between the start of the treatment and the date on which disease progression was first documented. Survival was measured from the date of the start of treatment to the date of death. Follow-up was measured from the date of the first treatment administration to the date of the last contact or death.

Statistical considerations

The primary end point of this study was to evaluate the safety profile of continuous oral capecitabine at fixed dose. Given that almost 20% of the patients would develop grade 3 or grade 4 toxicity with the standard 3-week capecitabine regimen, a sample size of at least 29 patients was required to verify a reduction of about 15% in grade 3–4 toxicity for a new treatment strategy, given α and β error probabilities of 0.05 and 0.20 (Simon's optimal design). It was planned to enroll at least 35 patients in the expectation of about 15–20% of unevaluable patients. Secondary end points were TTP and survival.

Results

Patient characteristics

Thirty-six patients were enrolled from October 2004 to December 2006. Baseline characteristics of the patients are presented in Table 1. Twenty-nine patients had CRC, and seven had gastric cancer. The median age was 81 years (range 76–85). In all, 28 of the patients (77.7%) had an Eastern Cooperative Oncology Group performance status of ≥ 1, 27 (75.0%) had liver metastases and 19 (52.7%) had multiple metastatic sites. Seven patients (19.4%) had received 5-FU-based adjuvant chemotherapy earlier, and six (16.6%) had received previous irradiation of the pelvis. No patient had received prior capecitabine. Combination regimen was not used because of patients' refusal (three fit patients), classification as vulnerable (24 patients) or frail (nine patients).

Treatment duration and toxicity

Two early discontinuations of treatment occurred before the end of the first month of chemotherapy because of patients' refusal to continue (one patient with colon cancer and bone fracture unrelated to treatment) and salvage surgical therapy (one patient with rectal cancer, not a progressive disease): these patients were not considered evaluable for toxicity and efficacy. A patient with gastric cancer discontinued treatment after 3 months because of reasons unrelated to adverse events; two patients with colon cancer were lost to follow-up after 3 and 5 months of treatment. One patient discontinued treatment because of persistent grade 2 HFS after 4 months of treatment. Two patients discontinued treatment because of liver function abnormality (grade 2, owing to the progression of liver metastasis) after 2 and 3 months of treatment.

Table 1 Patient characteristics

Characteristic	No. of patients ($n=36$)
Age, years	
Median (years)	81
Range (years)	(76–85)
≥ 80 years	21
Sex	
Male	23
Female	13
ECOG PS	
0	8
1	21
2	7
Primary tumor	
Colon	18
Rectum	11
Stomach	7
Metastatic sites	
Liver	27
Lung	7
Lypmh nodes	6
Local abdominal mass	15
Peritoneum	8
Bone	2
Resection	
Yes	24
No	12
No. of metastatic sites	
1	17
≥ 2	19
Previous adjuvant chemotherapy	7
Previous pelvic radiotherapy	6
Pain intensity	
0	8
1	19
2	7
3	2
Weight loss	
None	9
>10%	12

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

According to the Cockcroft and Gault equation, the baseline median creatinine clearance value was 47.8 ml/min (range 32.4–81.6 ml/min).

The median duration of treatment was 113 days (range 24–238 days); the median cumulative dose of capecitabine was 219 g (range 48–447 g) and the median dose intensity was 98%. The median BSA value of the enrolled patient cohort was 1.8 m^2, and the actual median dose intensity was 8080 mg/m^2/week. Assuming that the normal recommended schedules of capecitabine (2500 or 2000 mg/m^2/day for 14 days every 21 days) had been used, the maximum dose intensity should have been 11 666 or 9333 mg/m^2/week. Therefore, our population study received a dose intensity of capecitabine, which was approximately 31% less than the standard schedule and 13% less than the schedule usually used in elderly patients.

The common toxicities were HFS, diarrhea, fatigue and nausea/vomiting, the majority of which were grade 1 or 2 in severity (Table 2). No adverse-event-related deaths occurred during the study. No grade 4 toxicity or grade 3 hematologic toxicity was observed, and only 17.6% of the patients developed grade 1–2 neutropenia. Two patients (5.8%) experienced grade 3 adverse events: one CRC patient had grade 3 nausea and vomiting after 26 days of treatment, and one rectal cancer patient had grade 3 diarrhea after 57 days of treatment. Capecitabine was interrupted and then resumed with a dose reduction to 1500 mg daily in both cases.

Fatigue was observed (all grades) in 41.1% of patients, but it did not reach grade 3. Treatment was interrupted

Table 2 Worst occurrence of adverse events (34 evaluable patients)

	Grade 1	Grade 2	Grade 3
Hematological toxicity			
Neutropenia	4	2	–
Anemia	5	2	–
Thrombocytopenia	3	1	–
Nonhematological toxicity			
Nausea/vomiting	11	2	1
Diarrhea	14	3	1
Stomatitis	7	2	–
Hand–foot syndrome	13	4	–
Fatigue	11	3	–
Abdominal pain	2	–	–

owing to adverse events in seven patients (20.5%): the major causes for treatment interruption was diarrhea, HFS and fatigue. Dose reduction was needed in four patients (11.7%). Of the patients who had received pelvic radiotherapy earlier, two developed grade 2 diarrhea. No significant differences were observed in the incidence of each type of toxicity regarding the comorbidities and geriatric syndromes of the patients.

Treatment efficacy

The overall response rate in the 34 evaluable patients was 20.5% [95% confidence interval (CI): 0.10–0.36]. No patient achieved a complete remission. In all, 11 patients (32.3%) had stable disease (SD), whereas the remaining 16 patients (47.0%) had disease progression (Table 3). Responses were observed in six patients with CRC and in one patient with gastric cancer. SD was observed in nine patients with CRC and in two patients with gastric cancer.

In the subgroup of patients with metastatic CRC, the response rate was 22.2% (95% CI: 0.10–0.40), the median TTP was 4.4 months (95% CI: 3.3–5.5) and the median survival was 9.5 months (95% CI: 6.6–12.4). The patient with metastatic gastric cancer who achieved a partial response had 4.2 months of TTP, and survived for 7.6 months.

Discussion

In the current study, we evaluated the continuous oral administration of capecitabine at 2000 mg as a fixed daily dose in patients above 75 years with metastatic colorectal or gastric cancer, who had been considered ineligible for combination chemotherapy. The safety profile of capecitabine was very favorable: only 5.8% of patients developed grade 3 adverse events; any higher rate of toxic effects occurred in patients aged 80 years and above, who constituted 58.3% of study population. (Table 2).

The absence of grade 3–4 HFS and the very low rate of grade 2 HFS and grade 2–3 diarrhea might seem surprising. HFS and diarrhea were, however, virtually eliminated using a fixed-dose continuous schedule of capecitabine: this was also observed in a retrospective analysis that involved patients with different solid tumors [13].

In contrast, higher rates of grade 2–3 HFS (23%) and grade 2–3 diarrhea (20%) were reported by an earlier study involving metastatic CRC patients treated with continuous capecitabine at a daily dose of 1331 mg/m^2/day. The results of this small randomized phase II study led to the decision to adopt the cycling administration of capecitabine (2 weeks on and 1 week off) as the standard schedule, because it showed a longer median TTP over the continuous administration schedule [18].

Table 3 Response to treatment in 34 evaluable patients

	PR	SD	PD
Colon cancer	5	5	7
Rectal cancer	1	4	5
Gastric cancer	1	2	4

PD, progressive disease; PR, partial response; SD, stable disease.

A low rate (12%) of treatment-related grade 3 and 4 adverse events was observed by the Oncopaz Cooperative Group Study, which evaluated capecitabine 1250 mg/m^2 twice daily on days 1–14 every 3 weeks, in patients above 70 years, who had metastatic CRC [19]. The favorable safety profile in the Oncopaz study was likely due to the adjustment of the dose of capecitabine to 950 mg/m^2 twice daily, in patients with a creatinine clearance of 30–50. Other authors, nevertheless, reported that capecitabine was well tolerated among elderly patients when the dose of the drug was lowered to 1000 mg/m^2 twice daily, with about 10% of the patients presenting with grade 3–4 diarrhea and HFS [12,20].

A very low incidence (grade 1 in two cases) of HFS was also reported by a recent study that investigated continuous oral capecitabine in combination with oxaliplatin and pelvic radiation, in patients with locally advanced rectal cancer [21]. Another phase I study, performed on Japanese patients, investigated the use of continuous administration of capecitabine in solid tumors: the maximum tolerated dose was 1.255 mg/m^2 twice daily, and skin fissures and gastric ulcers were noted as the dose-limiting toxicities [22].

The safety profile of the capecitabine fixed dose in this study seemed more favorable than that reported in another study that investigated a fixed 2000-mg twice-daily dose of capecitabine on days 1–14 every 3 weeks: grade 2–3 toxic effects were diarrhea (34%), fatigue (27%), stomatitis (15%) and HFS (22%), and dose reductions were required in 29% of patients [23].

As regards other toxic effects, fatigue (all grades) occurred in 41.1% of our study population, but never reached grade 3. It was, however, difficult to distinguish cancer-related from treatment-related fatigue in many of these elderly patients.

Capecitabine treatment was highly tolerated in this study; despite this, a moderate renal impairment was demonstrated, with patients showing a median creatinine clearance of < 50 ml/min at baseline. Reductions of the starting dose of capecitabine are recommended in patients with moderate renal impairment. In line with this recommendation, therefore, our findings suggest that continuous capecitabine at a low fixed dose (e.g. 2000 mg/day) can be safely proposed for elderly patients, also

those above 80 years, most of whom have a physiological deterioration of renal function. Although a comparison with other reports is difficult because of the small sample size, the very low percentage of grade 2–3 adverse events in this study suggests that even a small reduction in the total daily dose can be sufficient to significantly reduce the main toxicities.

The analysis of dose intensity showed that it was approximately 31 or 13% less than the maximum dose intensity administered by the standard cycling 2 weeks on every 21-day schedule, at doses of 2500 or 2000 mg/m^2, respectively. Dose adjustment and delays were, however, very infrequent; therefore, it is reasonable to estimate that the actual dose intensity of capecitabine was close to that administered by the conventional schedule, and similar to that given by the 2000-mg/m^2/day cycling dose, which is often used in elderly patients [12,24].

Another point to consider is that the 1-week rest period reportedly appealed to patients, and it also maintained the efficacy of the capecitabine therapy [25]. Our results, however, with a median duration of treatment of 113 days, minimal interruptions and low rate of dose reductions, suggest that the simplification of administration and the low number of daily tablets might appeal to elderly patients, perhaps even more than the week of rest included in the conventional schedule of capecitabine. Our study population, which included very old patients, nevertheless, received full and detailed information about the oral treatment with capecitabine, and had regular phone contacts with nurses and physicians of the oncology units. This method might improve compliance and adherence to treatment in elderly patients, who often live alone.

With respect to efficacy, capecitabine produced a response rate of 22.2%, a median TTP of 4.4 months and a median survival of 9.5 months in the subgroup of patients with metastatic CRC (Table 3). These findings were similar to those usually observed with capecitabine as first-line therapy in patients of all ages with advanced CRC [26,27]. Although the studied populations are not completely similar with respect to age and capecitabine doses, the efficacy results of our study are comparable with those of the capecitabine 1250-mg/m^2 or 2000-mg twice-daily fixed-dose group (days 1–14 every 21 days; 24 and 28% response rates and 11.0 and 11.2 months of median survival, respectively) [19,23].

In the small subgroup of elderly patients with metastatic gastric cancer, partial responses or SD were observed in three patients, but the low number of cases did not permit any comparison with other studies.

In conclusion, this study suggests that continuous oral capecitabine at a fixed daily dose is well tolerated, and allows for simplification and ease of dosing in elderly patients with metastatic colorectal and gastric cancer.

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