

Salvage Treatment with Single-agent Capecitabine in Patients with Heavily Pretreated Advanced Colorectal Cancer

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Abstract. *Background: Refractory and/or relapsing advanced colorectal cancer (ACRC) requires frequent and prolonged hospitalisations, with a negative impact on the patients' quality of life (QoL). The aim of this single-centre, phase II study was to investigate the efficacy and safety of capecitabine (C) as salvage therapy in patients (pts) with ACRC, heavily pretreated with various chemotherapeutic regimens, as well as radiotherapy. Patients and Methods: A total of 28 pts were enrolled, with the following characteristics: 16 male and 12 female, median age 60 years (36-70) and median ECOG PS 1 (0-2). All pts had previously received at least 2 regimens of standard chemotherapy, including 5-FU/leucovorin, oxaliplatin and irinotecan in various combinations, while 8 pts had been offered radiotherapy. Four pts had already been treated with C. The treatment was administered at home and consisted of C at a dose of 1250 mg/m² twice daily on days 1-14, every 3 weeks, until disease progression (PD) and for a maximum of 9 cycles. Since grade (G) 3 gastrointestinal (GI) toxicity was observed among the first 7 pts, a daily dose of 2 g/m² was adopted in the subsequent enrolment. Results: The disease control (DC) rate was 53% (95% CI: 33.8%-72.5%): partial response in 2 pts and disease stabilization in 13 pts. Three out of 4 pts previously exposed to C showed stable disease. A significant symptom improvement was demonstrated in all 4 pts with non-measurable baseline disease. The median time to progression was 4 months (range: 2-7). Nine pts had PD while on treatment. The median overall survival times for pts with DC and PD were 6 months and 3 months, respectively. Various types of G3 haematological toxicity were observed in 4/28 pts, G3 hand-foot syndrome in 6/28 pts and G3 GI toxicity in 8/28 pts. Nevertheless, the*

patients' QoL and the regimen's safety profile were satisfactorily preserved. Conclusion: Despite its methodological limitations, our trial suggests that salvage treatment of heavily pretreated ACRC with single-agent C may be considered a safe and cost-effective alternative to best supportive care.

Advanced colorectal cancer (ACRC) is characterized by the presence of unresectable locally advanced disease and/or metastatic lesions. With best supportive care, the median survival time for patients with ACRC does not exceed 9 months. Despite the substantial improvement in clinical outcome with the recent introduction of newer cytotoxic agents, as well as targeted active agents, treatment in this setting is considered primarily palliative (1). The management of patients that have already been treated with most of the available standard regimens remains a challenge, since relapsing and/or refractory ACRC requires frequent and prolonged hospitalisations, having a negative impact on the patients' quality of life (QoL).

Capecitabine, an oral prodrug converted to fluorouracil (5-FU) preferentially in tumour cells by a sequential triple enzyme pathway, appears to mimic intravenous continuous-infusional 5-FU in terms of drug pharmacokinetics and activity. It has been evaluated as first-line treatment in ACRC, either as a single agent or combined with oxaliplatin and irinotecan. As monotherapy, it has demonstrated superior response rates, along with favourable safety, convenience and cost-effectiveness profiles when compared with the intravenous bolus 5-FU/leucovorin (LV) regimen, even in patients with prior adjuvant chemotherapy (1-3). It has also been evaluated in the setting of second- and third-line treatment, achieving disease stabilisation in a considerable proportion of patients (5-12).

The aim of this pilot, open-labelled, single-centre phase II study was to investigate the efficacy and safety of capecitabine as salvage therapy in patients with ACRC, heavily pretreated with various regimens including the same agent, as well as chemoradiotherapy. In addition to the above, the rationale for using capecitabine in these patients

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Table I. Patient characteristics (N=28).

	No. of patients	%
Sex		
Male	16	57
Female	12	43
Age (years)		
Median (range)	60 (36-70)	
ECOG PS		
Median (range)	1 (0-2)	
Time from diagnosis of ACRC (months)		
Median (range)	16 (12-20)	
Site of metastasis		
Liver	25	89
Lung	12	43
Other	17	60
Locally unresectable disease	2	7
Previous therapy		
Median number of treatments (range)	2 (2-3)	
5-FU/LV(bolus/continuous infusion)*	28	100
Irinotecan-containing regimen	20	71
Oxaliplatin-containing regimen	15	53
Capecitabine	4	14
Radiotherapy	8	29

Abbreviations: ACRC, advanced colorectal cancer; 5-FU, 5-fluorouracil; LV, leucovorin; ECOG PS, performance status according to the Eastern Co-operative Oncology Group scale.

*Given as either adjuvant or first line treatment.

included the known clinical benefit of second-line treatment with 5-FU when administered either as a continuous infusion following bolus regimens of the same drug, or as a rechallenge in case of ACRC relapse or progress after a long treatment interval (1, 2, 4).

Patients and Methods

The trial was conducted from September 2001 to September 2002. A total of 28 patients with ACRC were enrolled. Their demographic and baseline characteristics are summarized in Table I. All patients had a life expectancy of at least 3 months, an ECOG performance status of less than 3 and adequate bone marrow reserves. All had previously received at least 2 regimens of standard chemotherapy, including 5-FU/LV, capecitabine, oxaliplatin and irinotecan in various combinations and sequencing, while 8 patients with rectal cancer had also been offered radiotherapy (Table I). The disease had progressed or relapsed while on chemotherapy or within 3 months after completing the last therapeutic intervention. In the case of 4 patients, who had already been treated with capecitabine, a relapse interval of at least 6 months was a prerequisite for their enrolment.

According to the study design, capecitabine would be administered at a dose of 1250 mg/m² twice daily on days 1-14, every 3 weeks, until disease progression or unacceptable toxicity or patient refusal for further treatment and for a maximum of 9 cycles (6 months). Treatment-related adverse events of grade 3 (as defined by the NCI common toxicity criteria), mainly consisting of nausea

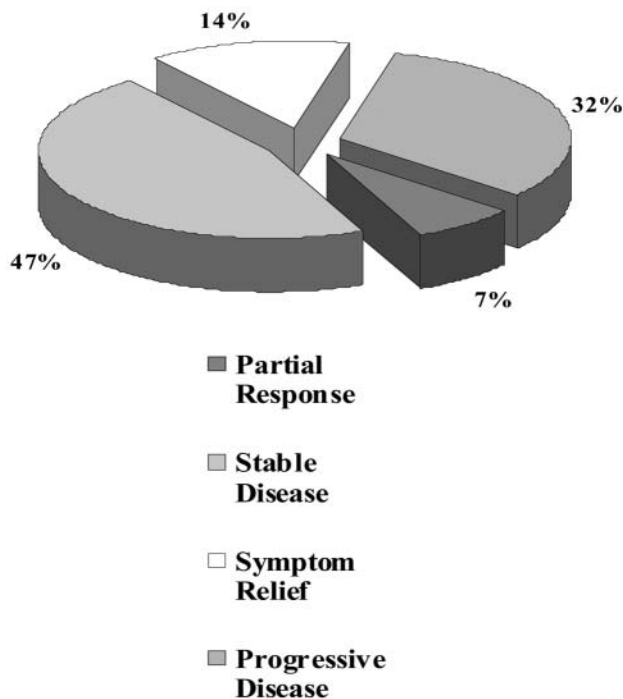


Figure 1. Distribution of patients according to the response to capecitabine monotherapy.

and diarrhoea, were observed among the first 7 patients, leading to a 20% dose reduction after resolution of the toxicity. The modified daily dose of 2000 mg/m² in 2 divided doses was adopted in the subsequent accrual. The patients were treated at home. Study visits were performed after every 2 cycles or more often as indicated, while tumour assessment by imaging was repeated every 2 cycles. The median follow-up period was 9 months (range: 3-12).

Results

A total of 156 cycles were administered, with a median of 5 cycles per patient (range: 3-9). All 28 patients were assessable for both response and toxicity. No complete response was noted. A partial response was obtained in 2 patients (7%, 95% CI: 0.09%-23.5%) and disease stabilization in 13 patients (46%, 95% CI: 27.5%-66.1%), leading to an overall disease control rate of 53% (95% CI: 33.8%-72.5%). The median time to progression was 4 months (range: 2-7). Three out of 4 patients previously exposed to capecitabine showed stable disease. A significant symptom improvement was demonstrated in all 4 patients with non-measurable baseline disease, such as peritoneal carcinomatosis, who were considered as having stable disease. Nine patients (32%) experienced disease progression while on treatment (Figure 1). The median overall survival time for the population under study reached 5.2 months (95% CI: 3.1 to 7.3 months). The median overall

Table II. Activity of single-agent capecitabine in patients (pts) with heavily pretreated ACRC.

	(n=28)
Disease control* (%)	53
95% Confidence interval	33.8-72.5
Partial response (PR) (%)	7
95% Confidence interval	0.09-23.5
Disease stabilization (SD) (%)	46
95% Confidence interval	27.5-66.1
Symptom relief** (%)	14
Disease progression (%)	32
Time to progression (months)	4
Range	2-7
Overall survival (months)	
Median	5.2
95% Confidence interval	3.1-7.3
-For pts with disease control (median)	6
-For pts with progressive disease (median)	3

*Includes complete response, PR and SD.

**Pts with non-measurable baseline disease, included in pts with SD.

survival times for patients achieving disease control and for those progressing were 6 months and 3 months, respectively (Table II).

The majority of treatment-related adverse reactions were mild or moderate (Table III). Although most of them had been anticipated, the corresponding rates were relatively high compared to the ones reported for the use of capecitabine as first-line monotherapy in ACRC (2). Nevertheless, no hospital admissions were required, nor did any toxic deaths occur. The most prominent grade 3 side-effects are summarized in Table III. Despite toxicity, the patients' quality of life (QoL) and the regimen's safety profile were satisfactorily preserved.

Discussion and Conclusion

During the last decade, the therapeutic options for the first-, as well as the second-line, treatment of ACRC have increased impressively, offering a significant survival benefit for patients with this condition. The median life expectancy has been extended to the range of 20 months when all available effective cytotoxic agents, including fluoropyrimidines, irinotecan and oxaliplatin, are administered during the course of the disease, either in combination or as sequential therapy. An additional advance in the overall survival is awaited with the advent of the novel biological agents, bevacizumab and cetuximab. As the therapeutic modalities mentioned above may significantly retard disease progression, the use of third- or even fourth-line treatments has become possible (1).

Table III. Treatment-related toxicity.

Adverse reaction	All grades*(%)	Grade 3 (%)
Hand-foot syndrome	89%	21%
Diarrhoea	75%	25%
Nausea	36%	29%
Vomiting	11%	4%
Abdominal pain	21%	7%
Anaemia	79%	7%
Neutropenia	42%	4%
Thrombocytopenia	21%	4%

*According to NCI (National Cancer Institute) common toxicity criteria.

It seems that the oral fluoropyrimidines, namely capecitabine, have advantages over intravenous 5-FU with regard to convenience of administration, tolerability, tumour cell selectivity and inhibition of resistance mechanisms. Single-agent capecitabine produces response rates of up to 27% in untreated ACRC and is strongly recommended in patients in whom fluoropyrimidine monotherapy is indicated (1-3). Phase II trials evaluating capecitabine in the setting of refractory ACRC, either as monotherapy or combined with other cytotoxic agents such as mitomycin, yielded conflicting results regarding its efficacy (5-12).

At the time our trial was designed, biologically-targeted therapies for ACRC were not available. The rate and duration of disease response were selected as the primary end-points, since overall survival is influenced not only by the treatment undertaken, but also by biological determinants and subsequent therapeutic interventions. According to the results of our study, single-agent capecitabine given as a third- or even fourth-line treatment may have a favourable impact on the clinical outcome of ACRC, mostly in terms of disease control, while preserving the patients' QoL. Although one could argue that patients with less aggressive disease will survive longer regardless of the number and type of treatments received, the survival times for the patients enrolled in our study compare favourably with those expected for such a poor-prognosis population. The efficacy of capecitabine was maintained despite dose modification for adverse events. Apparently, the interpretation of the results presented above should take into account the unavoidable heterogeneity of the patients enrolled, in terms of tumour burden, site of metastasis and previous treatment. Unfortunately, the small sample size did not allow for subgroup analysis.

Despite its methodological limitations, our study clearly suggested that salvage treatment of heavily pretreated ACRC with single-agent capecitabine may be considered a

convenient, safe and cost-effective alternative to best supportive care. Interestingly, a proportion of patients seem to retain capecitabine sensitivity and may enjoy clinical benefit with the drug rechallenge. Combination of capecitabine with the newer biological agents in the particular setting might further improve disease outcome. Evaluation through larger, randomized clinical trials is warranted.

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