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ORIGINAL ARTICLE

Capecitabine as third line therapy in patients with advanced colorectal cancer

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Abstract
This study sought to determine whether third line therapy with capecitabine (cap.) could provide any clinical benefit in patients with advanced colorectal cancer who have progressed on 5-Fu combination therapy with both irinotecan and oxaliplatin. Twenty patients who were pretreated with and had progressed on irinotecan + Nordic FLv (5-Fu/leukovorin) and oxaliplatin + c.i. 5-Fu/leukovorin were studied. Cap. was administered at 1000–1250 mg/m^2 bid d1-14 q 3 w. Time to progression (TTP) (either radiological or clinical) and overall survival (OS) were estimated with the Kaplan-Meier actuarial method. The median number of administered cap. courses was four. No radiological or biochemical responses were observed. Three patients were classified as having stable disease at three months. Two of these patients had, however, minor radiological progression and a $\geq$100% increase in CEA compared to base line. Seventeen patients were classified as having progressive disease during the first three months period. Median TTP and OS were 2.8 months and 6.1 months, respectively. A response rate of $\geq$15% for third line cap. in metastatic CRC can be ruled out. Median PFS was limited in the study population. This observation and the few cases with SD at three months, lead us to believe that little or no clinical benefit can be expected from single drug cap. in patients with irinotecan- and oxaliplatin-combination resistant advanced colorectal cancer.

Introduction

Ultimately, metastases develop in 35% to 50% of patients who have undergone surgery for colorectal cancer (CRC) in Western Countries [1]. For many years, 5-Fluorouracil (5-Fu) in various schedules has been the dominating agent in the treatment of recurrent CRC. With the introduction of new agents, i.e. irinotecan and oxaliplatin, during the last few years, the treatment of metastatic CRC has become more complex. Furthermore, therapy with 5-Fu alone has been in common use in the adjuvant setting until recently. Currently, there is a process for introducing new agents as oxaliplatin in the adjuvant setting [2]. Studies are also underway concerning the efficacy of irinotecan as an adjuvant to surgery [3]. This process will ultimately lead to a considerable increase in the number of patients with recurrent CRC who have been pretreated with irinotecan or oxaliplatin in combination with infused or bolus 5-Fu in the adjuvant setting. This change in treatment strategy raises the question of third line therapy in patients pretreated with irinotecan, oxaliplatin and 5-Fu/leukovorin (Lv).

Currently, selected patients in good physical condition with tumors resistant to combination therapy with irinotecan/5-Fu/Lv and oxaliplatin/5-Fu/Lv receive treatment with capecitabine in some centers. The oral intake of capecitabine for two weeks per course resembles the prolonged effect of infusional 5-Fu. Furthermore capecitabine is activated through a three-step process into 5-Fu resulting in higher concentrations of 5-Fu in tumor cells compared to normal cells [4]. Cases of tumor response to capecitabine in patients with tumors resistant to 5-Fu have been reported [5]. Responses to capecitabine in 5-Fu resistant tumor cell lines in preclinical trials have also been published [4,6]. These reports

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and the good tolerability of the drug make it an acceptable choice for third line therapy in highly treatment motivated patients. Little is, however, known about the efficacy of capecitabine as third line treatment of metastatic CRC in large treatment series.

The objective of this trial was to evaluate retrospectively the efficacy of single agent capecitabine in patients with metastatic CRC who had progressed on treatment with irinotecan in combination with bolus 5-Fu/Lv and oxaliplatin in combination with infusional 5-Fu/Lv.

Material and methods

The ethical committee at the Karolinska Institutet, Stockholm, has granted permission for this retrospective study.

The patients were identified through a retrospective review of all patients with metastatic CRC treated at the Department of Oncology at Karolinska University Hospital Huddinge in Stockholm during the period 2000 to 2004. Patients who had been treated with capecitabine as third line therapy as a palliative treatment after progression on first and second line treatment were selected for the analysis. Patients who were treated with any other drug combination than 5-Fu/Lv alone in adjuvant setting were not included.

The patient population consisted of 20 patients, 11 male and nine female. The median age was 65 years ranging from 42 to 78. All patients had metastatic CRC with the most common metastatic sites being the liver (no 13) and the lung (no 8). The number of metastatic sites per patient varied from one in nine cases, to two in nine cases and three in two cases.

All patients had received first line palliative therapy with FLIRI {irinotecan (180 mg/m^2 d1) in combination with Nordic FLv (bolus 5-Fu 500 mg/m^2 and leukovorin 60 mg/m^2 d1-2), q2 weeks}. All patients had progress on FLIRI and were fit to proceed to second line treatment with the simplified/modified FOLFOX 4 regimen (oxliplatin 85 mg/m^2 d1 and bolus 5-Fu 400 mg/m^2 d1 and leukovorin 200 mg/m^2 d1, followed by infusional 5-Fu 2400 mg/m^2 during 46 hours d1-2, q2 weeks). Both lines of treatment had been monitored for efficacy radiologically according to the WHO or the RECIST criteria and biochemically, i.e. CEA, every third to fourth month.

All patients selected to receive capecitabine as third line treatment had good overall functional level (WHO status $\leq$2) and good liver-, bone marrow- and kidney functions (maximum level of plasma creatinine of 120 μmol/l and serum bilirubin of 40 μmol/l). Capecitabine was administered at the dose of 1000 – 1250 mg/m2 bid d1-14, q3 weeks. Kidney-, liver- and bone marrow functions were monitored through blood samples at the beginning of every course of capecitabine, as was the patients' performance. Adverse events were routinely registered in the patient files and graded according to CTC-criteria [7]. Tumor size was evaluated radiologically, typically less than one-month prior to start of capecitabine with either computer tomography or magnetic resonance tomography. Tumor response was subsequently assessed by the use of the identical radiological method after three months of treatment and scored according to the RECIST criteria [8].

Complementary biochemical assessment with CEA was used in the majority of cases. CEA samples were taken at the beginning of therapy and at three months intervals during capecitabine therapy. Although CEA was monitored it did not influence the radiological evaluation of tumor response. Four patients were classified as having progressive disease on clinical grounds and were not evaluated radiologically due to rapid deterioration of their health.

To test the probability of the observed response rate if the true response rate was greater than 15% the binomial exact test was used. Time to progression (TTP) and overall survival (OS) were estimated with the Kaplan Meyer actuarial method [9].

Results

No radiological response was detected (95% CI 0 – 13.9%) in the studied patient population. Three patients were reported to have a radiologically stable disease (SD) after three months of single agent capecitabine. However, two of these patients had at the time of the first evaluation, an increase in CEA $\geq$100% compared to baseline. In the third patient with SD, the radiological evaluation corresponded to a stabilization of CEA. In all three patients with radiologically SD, the treatment with capecitabine continued for another three months. After six months of treatment only one patient continued to show radiologically SD. However, the CEA level had in this case increased with 42%. This patient had bone metastases only and was the one to demonstrate both radiological and biochemical response at three months of treatment.

The median number of administered capecitabine courses given in the entire population was four. The patient registered with SD at three and six months of treatment received a total amount of 12 courses and was then classified as having progressive disease.

Side effects of grade 1-2, 3 and 5 were recorded in seven, two and one cases, respectively. The most

common adverse events were hand-foot syndrome and diarrhea. Four cases of serious infectious episodes requiring admission to hospital were registered. One patient died during course number 2 due to rapid deterioration following an episode with febrile neutropenia and his death was probably treatment related.

Median time to progression (TTP) was calculated to 2.8 months (85 days). Median overall survival (OS) was assessed according to the Kaplan Meyer actuarial method to 6.1 months (185 days). The TTP and OS curves are shown in Figure 1.

Discussion

A response rate greater than 15% can be ruled out for capecitabine as third line treatment in FLIRI and simplified/modified FOLFOX 4 resistant metastatic CRC with respect to the number of patients in this retrospective study. In this patient series, third line capecitabine was associated with one case of treatment related death and four hospitalizations due to infectious complications. Furthermore, the short median TTP and few cases of stable disease at first evaluation were obvious. It is noticeable that despite the short median TTP in the studied population, the median OS was relatively long (Figure 1). This was probably due to patient selection mechanisms and not caused by a positive therapeutic effect of capecitabine.

Since the introduction of 5-Fu in 1957, it has become well established in the treatment of metastatic CRC. Response rates ranging up to 30% have been reported. The uptake of oral administration of 5-Fu was early proven to be clinically unforeseeable considering the fact that less than 75% of the dose reached the systemic circulation and the huge variety of plasma levels observed in different patients. This led to the development of 5-Fu as an intravenous drug and further investigation of pros and cons of bolus and continuous administration. The development of capecitabine, which through an intracellular activation is transformed into 5-Fu and by prolonged oral intake resembles the infusional administration of 5-Fu provided during recent years a new alternative to the traditional use of bolus 5-Fu. High tolerability of this drug has been reported in chemonaive patients [10]. The activation of capecitabine, leading to higher concentrations of 5-Fu in tumor cells than in normal cells, might be the theoretical background for the good tolerability and effect equaling intravenous 5-Fu. These facts did, however, not appear relevant in the studied pre-treated population suggesting that tumor resistance to 5-Fu is mediated by intracellular factors rather than uptake of 5-Fu into tumor cells.

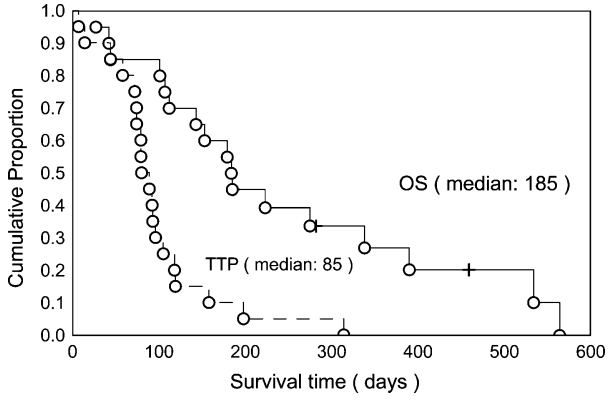

Figure 1. Median TTP and median OS in patients with irinotecan- and oxaliplatin-combination resistant advanced colorectal cancer receiving capecitabine as 3rd line therapy.

Recently, single agent capecitabine in patients with metastatic CRC refractory to 5-Fu has been reported to show no objective responses, although stable disease was reported in 50% of cases [11]. This suggested a modest clinical benefit in 5-Fu refractory tumors at the most.

Considering the limited impact of capecitabine in this study, although small and retrospective in nature, monoclonal antibodies like cetuximab and bevacizumab seem more promising as third line treatment for patients with metastatic CRC. However, capecitabine has been shown to be active in palliative treatment of advanced CRC and in the adjuvant setting [10,12]. Furthermore, it has become an alternative to 5-Fu in combinations with other agents, such as oxaliplatin and irinotecan, establishing itself in the treatment of CRC [13].

The lack of response to capecitabine and the short TTP in the studied population lead us to conclude that little or no clinical benefit can be expected of this drug in heavily pretreated patients. Furthermore, a considerable amount of severe side effects were observed.

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