

Capecitabine for Treatment of Advanced Hepatocellular Carcinoma

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Short Title: Capecitabine for HCC

Key words: Capecitabine, hepatocellular carcinoma, chemotherapy

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Abstract

Background

Patients with advanced hepatocellular carcinoma (HCC) face a dismal prognosis, as no effective palliative chemotherapy exists. Moreover, treatment of patients with hepatocellular carcinoma presents a major challenge, because associated cirrhosis limits the choice of chemotherapeutic agents. We evaluated the activity and toxicity of capecitabine in patients with advanced hepatocellular carcinomas.

Methods

The authors performed a retrospective analysis of all patients with HCC who were treated with capecitabine. The medical records of patients with HCC who were treated at our institution between October 2002 and July 2005 were reviewed.

Results

A total of eleven patients were treated with capecitabine. Eight patients had liver cirrhosis and Child-Pugh scores of A and B. Capecitabine was administered twice daily for 14 days at a total daily dose of 2000 mg/m². Treatment was repeated every 21 days. Each patient received 2-16 treatment cycles. One partial response was observed (9%; 95% confidence interval (CI) 0.2–41.3%) and 3 month progression free survival rate was 27%. The median time to tumor progression and median overall survival were 2.2 months (95% CI 1.7–2.7 months) and 10.1 months (95% CI 3.0–17.2 months), respectively. The therapy was well tolerated, with hand-foot syndrome as the main toxicity. Grade 3 diarrhea occurred in one patient. Grade 3/4 hyperbilirubinemia was seen in five patients, but was mainly due to tumor progression. No other significant toxicities were observed.

Conclusions

Capecitabine was found to be safe for treatment of patients with HCC, including those with compensated cirrhosis. However, the objective response rate was limited.

Background

Hepatocellular carcinoma (HCC) is a malignancy of worldwide significance. HCC is the fifth most common solid tumor worldwide and is currently considered as the fourth leading cause of cancer-related death [1]. The majority of new cases occur in developing countries, especially in Asia and Southern Africa, but the incidence is increasing in the western world, including Japan, Western Europe, and the United States [2,3].

HCC is typically diagnosed late in the course of patients with chronic liver disease, with the median survival following diagnosis of approximately 6 to 20 months [4]. With exception of the southern African black population [5] it arises as a complication of long-standing liver cirrhosis mainly caused by hepatitis B or C viral infections or increased alcohol intake [6].

Even though the mainstay of therapy is surgical resection or liver transplantation, several other treatment modalities including local ablative therapies and chemoembolisation may also have a role in selected patients [7]. The usefulness of cytotoxic chemotherapy or hormone agents for treatment of advanced disease has been evaluated by a large number of clinical trials. Nevertheless, only few studies have been able to show response rates of more than 20% [8]. As a result no standard chemotherapy regimen for advanced disease exists. Moreover, liver cirrhosis may be as limiting as the malignancy itself. Consequent hepatic dysfunction complicates safe administration of systemic therapy [9].

Capecitabine is an orally administered systemic prodrug, that crosses the gastrointestinal barrier intact and is rapidly and almost completely absorbed. It is converted to its only active metabolite, 5-fluorouracil (5-FU), by thymidine phosphorylase. There are higher levels of this enzyme in several tumors and the liver, compared with normal healthy tissue. The predominant route of elimination is renal. Capecitabine has shown varying degrees of antitumor activity with acceptable tolerability in numerous cancers, with the largest amount of evidence in metastatic breast and colorectal cancer [10]. A recent study indicated that mild-to-moderate liver dysfunction in patients with colorectal carcinoma liver metastases did not significantly affect capecitabine pharmacokinetics. Therefore, patients with such liver dysfunction should be monitored closely during treatment, but no dose adjustment solely on the basis of this condition is required [11].

On the basis of these results we treated patients with HCC and no other treatment option with capecitabine. These patients were not eligible for surgery, local ablative therapies or chemoembolisation because of advanced tumors or impaired liver function. Now, we performed a retrospective analysis of the efficacy and toxicity of this regimen. Herein we report the results of this analysis.

Materials and Methods

Patients

A manual retrospective review of medical records for the time between October 2002 and July 2005 was performed, and 11 patients with HCC who received “off-protocol” treatment with capecitabine were identified at our institution (Department of Internal Medicine II, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany). During that period, systemic chemotherapy was offered to patients who did not qualify for resection or liver transplantation and who were not eligible for local

ablative therapies or chemoembolisation. Patients were informed about the “off-label” use of capecitabine. All patients received information regarding the potential benefits and side effects associated with the agent. Informed consent was obtained from all patients prior to therapy. The retrospective analysis was approved by local ethics committees.

Capecitabine was offered to patients who had a performance status (WHO) ≤ 2 , an absolute leukocyte count $\geq 3.5 \times 10^9/L$ and a platelet count $\geq 75 \times 10^9/L$. Laboratory studies were performed to ensure that patients met the following additional criteria: serum creatinine levels ≤ 2.0 mg/dL and total bilirubin levels ≤ 5.0 mg/dL.

Capecitabine treatment was offered regardless of whether patients had been treated previously with other agents or radiotherapy. Patients with decompensated cirrhosis (Child-Pugh C) and women who were pregnant or breastfeeding were ineligible for the treatment.

Treatment Plan

Therapy was administered on an outpatient basis. Capecitabine (Xeloda; Roche Laboratories) was administered orally twice daily at a dosage of 2000 mg/m² per day for 14 consecutive days followed by 7 days of rest. This cycle was repeated every 21 days. Doses were reduced by 25% or 50% depending to the general condition of the patient, serum bilirubin value, and platelet count if necessary.

Patient Evaluation

Before each treatment course, all patients gave a complete medical history and underwent a physical examination. Before each cycle a complete chemistry panel was obtained. Toxicity was monitored using National Cancer Institute Common Toxicity Criteria for Adverse Events, version 2.0 (NCI CTCv2.0). The registration period for adverse events included 28 days after discontinuation of capecitabine. Unless signs of progression were evident, the antitumor response was evaluated every three months by computed tomography (CT) scan, magnetic resonance imaging or, if applicable, ultrasonography.

According to RECIST criteria complete response was defined as the disappearance of all signs and symptoms of disease. Partial response was defined as a decrease of $>30\%$ of the sum of the largest diameters of target (=measurable) lesions without appearance of new lesions or progression of non-target (=evaluable) lesions. To be assigned a status of response, changes in tumor measurement were confirmed by repeat assessment that was performed no less than 4 weeks after the criteria for response were first met. Stable disease was defined as no sufficient shrinkage to qualify for partial response or less than a 20% increase in the sum of the largest diameters of target lesions without appearance of new lesions or progression of non-target lesions. Progressive disease was defined as a 20% increase in the sum of the largest diameters of target lesions or as appearance of new lesions or as progression of non-target lesions.

Objective responses were validated by radiologists independent of the study. The time to disease progression and overall survival were calculated from the date of initiation of therapy to the date of progression of disease or death, respectively.

Statistical Methods

The objective of the current study was to collect all pertinent clinical information regarding patients with HCC who were treated with capecitabine during the period

between October 2002 and July 2005. All available patients with HCC who had ever received any dose of capecitabine were included in the analysis.

Baseline laboratory markers were expressed as median values with ranges. Progression free survival and overall survival were analysed by the Kaplan-Meier method. 95% confidence intervals (CI) for rates were calculated by the method of Clopper and Pearson. All tests were performed two-tailed with $p < 0.05$ indicating statistical significance. For data management and statistical analysis, SPSS software (SPSS Inc., Chicago, IL), version 13.0, was used.

Results

Patient Characteristics

Eleven patients – eight men and three women – treated during the 3-year study period were included in the current analysis. Their pre-treatment characteristics are listed in Table 1. The median age was 65 years (range 55–75 years). Histologic confirmation of HCC was present for eight patients. For the remaining three patients HCC was diagnosed noninvasively based on typical appearance in a cirrhotic liver on radiologic imaging combined with the presence of a serum AFP >400 ng/mL as defined by consensus criteria [12]. All three patients had an AFP of minimum 3180 ng/mL.

Eight patients had liver cirrhosis and four of them a history of alcohol abuse. Chronic hepatitis B was present in one and chronic hepatitis C in two patients. One patient (9%) had relapse of disease after surgery. Two patients (18%) had been previously treated with transarterial hepatic chemoembolisation and three patients had received previous systemic therapy. All other patients were chemotherapy-naïve. None of the patients had been exposed to radiotherapy.

Baseline AFP levels were recorded in all eleven patients and were elevated in ten of them with AFP >400 ng/mL in six patients (median 755, mean 16,028, range 5.5–112600; normal <6 ng/mL). The majority of patients had advanced tumor stages and unfavourable prognostic scores. Five patients were classified Okuda stage II and eight had an advanced CLIP score (1998) of two or more.

Toxicity

A total of 49 cycles were administered during the trial (median 3 cycles; range 2–16 cycles). Six patients received a full starting dose, three patients were treated with a dose reduced by 25% and two with a dose reduced by 50%. Overall, capecitabine was well tolerated (Table 2). No treatment-related deaths occurred.

Myelosuppression was mild. Two patients developed anemia with a minimal hemoglobin of 8.1 mg/dl and received erythrocyte transfusions. Nausea and emesis, when present, usually were mild. Grade 3 diarrhea was present in one patient and resolved to grade 1 under treatment with loperamid. Grade 3 hand-foot skin reaction occurred in 2 patients, but was manageable by topical treatment during the further course. Dyspnea on exertion observed in two patients was due to pleural effusion and heart failure, respectively.

The documented raise in bilirubin levels was mainly seen after discontinuation of capecitabine and is therefore most likely due to tumor progression and not treatment-related.

Response and survival

No complete response was observed. One female patient (9%; 95%CI 0.2–41.3%) had a partial response confirmed by CT scan, which lasted 13.3 months from begin of therapy. Two additional patients (18%; 95%CI 2.3–51.8%) had stable disease for a duration of 3.7 and 4.6 months. The remaining eight patients had progressive disease.

Median progression free survival was 2.2 months (95% CI 1.7–2.7 months) with a 3-month progression free survival rate of 27.3%. Median overall survival for all eleven patients was 10.1 months (95% CI 3.0–17.2 months) with a 6 and 12-month survival rate of 53.3% and 26.7%, respectively (Figure 1).

Discussion

Despite the advances in diagnostic techniques for HCC, the number of surgical candidates remains limited because of the advanced stage of HCC and poor hepatic reserve function at the time of diagnosis. For the majority (>80%) of patients there are several, but only palliative treatment options. Statistically significant evidence of improvement in survival as demonstrated in prospective controlled trials, is scarce [9]. In two recently published studies HCC patients were randomly assigned to receive repeated transarterial hepatic artery embolization versus supportive care. There was a modest improvement of survival for treated patient who had small tumor burdens, good performance status, and preserved liver function [13,14,15]. However, only a minority of evaluated HCC patients is suitable for this treatment. Systemic treatment includes the administration of hormone agents or cytotoxic chemotherapy. At present, both treatment modalities only show marginal response rates and no clear survival benefit.

Moreover, the administration of chemotherapy to patients with liver impairment results in complicated safety issues. Although caution in treating all patients with hepatic failure is essential, the use of certain agents provokes greater concern than others. Capecitabine appears to be relatively well tolerated [16]. This is demonstrated by a small number of studies that indicate the safeness of capecitabine for patients with mildly to moderately impaired hepatic function [11]. There is only one also retrospective study by Patt et al. to date about the use of capecitabine for hepatobiliary cancer containing 37 patients with HCC [17]. In that study palmar-plantar erythrodysesthesia was the most common side effect while hematologic toxicity was mild. These findings go along with our results. We observed grade 3/4 hand-foot skin reactions in two patients (18%) and there was no hematologic toxicity worth mentioning in our study. The elevation of bilirubin levels mainly occurred in the 28-day post treatment phase and was due to underlying tumor progression.

The good tolerability of capecitabine in patients with compensated cirrhosis in our study was limited to Child-Pugh Class A and B as well as in the preceding study by Patt. It has to be kept in mind, that these results cannot be extended to patients with decompensated cirrhosis (Child-Pugh Class C). Our results confirmed, that toxicity of capecitabine in patients with compensated cirrhosis lies within the same range, when used in patients with normal hepatic function [10].

At specialized centers the majority of patients with HCC present with advanced tumor stage and poor prognosis [18]. All patients included in the present analysis had advanced tumors without the possibility for a surgical approach or transarterial hepatic artery embolization. Consequently, the majority of our patients (73%) presented with an advanced CLIP score (1998) of two or more. In one study, median survival rates were 13, 8 and 2 months in patients with CLIP Stages 2, 3 and 4,

respectively [19]. Median survival observed in our study was 10,1 months suggesting no survival advantage for patients with HCC treated with capecitabine, but comparisons are inconclusive. Overall, these results do not support the use of capecitabine for treatment of patients with advanced HCC.

In our study an objective response rate of only 9% was observed. This is corresponding with a response rate of 11% (4 out of 37) in patients with HCC treated with capecitabine as reported by Patt and colleagues. The study of Patt et al. has to be considered negative on the assumption of a Simon MinMax Two Stage study design [20] considering a response rate of $\leq 5\%$ of a bad drug versus a response rate of $\geq 20\%$ of a good drug with a significance level of 0.05 and a power of 88%. Pooled analysis of our data and that of Patt et al. comes to a response rate of 10% (5/48, 95%CI 4–23%). Given this case pooled analysis would still result in a negative study according to the same Simon MinMax Two Stage design with an elevated power of 93%. These results are not superior to those of most published studies of systemic chemotherapy for HCC reporting response rates of 0% to 25% [9].

Conclusions

In conclusion, in this small group of patients capecitabine could be safely administered in patients with advanced HCC including those with compensated cirrhosis in an outpatient setting. Adverse events observed in this analysis were mostly complications of HCC and liver cirrhosis and otherwise in the expected range of that observed in patients without liver impairment. However, in terms of objective response antitumor activity observed in this study and of a pooled analysis with published data was only marginal.

Competing interests

The authors declare that they have no competing interests.

Authors` contributions

SvD carried out the care of the patients, collection and interpretation of the data, and drafting of the manuscript. CL conceived of the study, and participated in its design and coordination. MM and KS participated in patient care and coordination. ES F participated in its design and coordination. RMS helped to draft the manuscript and to interpret the results. FE conceived of the study, participated in its design and coordination and carried out the statistical analysis. All authors read and approved the final manuscript.

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Tables

Table 1. Patient Characteristics.

Table 1. Patient Characteristics

No. of patients	11
Sex	
Male	8 (73%)
Female	3 (27%)
Age (years)	
Median	65
Range	55-75
ECOG performance status	
0	3 (27%)
1	7 (64%)
2	1 (9%)
Hepatitis virus infection	
HBV	1 (9%)
HCV	2 (18%)
Cirrhosis	8 (73%)
Child-Pugh score	
A	5 (45%)
B	3 (27%)
Okuda stage	
I	6 (55%)
II	5 (45%)
CLIP score	
0	1 (9%)
1	2 (18%)
2	3 (27%)
3	2 (18%)
4	3 (27%)
Previous treatment	
Surgery	1 (9%)
TACE	2 (18%)
Chemotherapy	3 (27%)
Extrahepatic disease	3 (27%)
Pretreatment chemistries	
Total bilirubin (mg/dl)	
Median	1
Range	0.4-3.3
Aspartate aminotransferase (10-50 U/l ^a)	
Median	40
Range	8-779
Albumin (mg/dl)	
Median	3.7
Range	3.4-4.1
AFP (<6 ng/ml ^a)	
Median	755
Range	5.5-112600
Leukocytes (G/l)	
Median	6.9
Range	5.6-8.7
Platlets (G/l)	
Median	196
Range	91-360

ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; HCV: hepatitis C virus; CLIP: Cancer of the Liver Italian Program (1998); TACE: Transarterial hepatic chemoembolisation

^aConsidered normal levels at the study institution.

Table 2. Adverse events including 28 days after end of treatment.

NCI-CTC Grade	Number of patients (%)			
	1	2	3	4
Leukopenia	1 (9)	1 (9)	0	0
Neutropenia	1 (9)	0	0	0
Anemia	1 (9)	3 (27)	0	0
Thrombocytopenia	0	2 (18)	0	0
Diarrhea	3 (27)	0	1 (9)	0
Nausea/emesis	1 (9)	0	0	0
Stomatitis	1 (9)	2 (18)	0	0
Hand-foot skin reaction	2 (18)	2 (18)	2 (18)	0
Fatigue	3 (27)	2 (18)	0	0
Dyspnea	0	2 (18)	0	0
Flatulence	2 (18)	0	0	0
Hyperbilirubinemia	1 (9)	3 (27)	3 (27)	2 (18)
Raise in creatinine	2 (18)	0	0	0

NCI-CTC: National Cancer Institute Common Toxicity Criteria

Figures

Figure 1. Probability of progression free survival (dotted line) and overall survival for all eleven patients.