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ORIGINAL ARTICLE

Capecitabine and oxaliplatin (XELOX) as first-line treatment for patients with metastatic colorectal cancer

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Summary

Purpose: *For almost 40 years, 5-fluorouracil (5-FU) had been the only drug with demonstrated activity against (CRC), commonly used in combination with leucovorin (LV). Oxaliplatin and capecitabine are two relatively novel drugs used in the treatment of CRC. These drugs have been found to act synergistically, both in vivo and in vitro and their combination (XELOX) is highly active in metastatic colorectal cancer (mCRC). The aim of this study was to determine the safety and efficacy of XELOX in patients with mCRC.*

Methods: *The study endpoints were response rates, toxicity, progression free (PFS) and overall survival (OS). XELOX was administered as first line treatment to patients with mCRC. Patient selection criteria included histological confirmation of mCRC, ECOG performance status (PS) ≤2, and adequate bone marrow, renal and hepatic function. Patients received oxaliplatin 130 mg/m^2 i.v., day 1, and oral capecitabine 1000 mg/m^2 twice daily, days 1-14, every 3 weeks.*

Results: *34 patients were treated with XELOX; males/females 23/11, median age 53.5 years (range 42-65), ECOG PS 0/1 52%/48%. Metastatic sites were the liver (23/34; 67%), lung (7/34; 20%), and bone (4/34; 11%). No patient achieved complete response (CR), 14 patients showed partial response (PR), 8 stable disease (SD) and 11 progressed (PD). Median PFS was 5.5 months, median OS 12.9 months and 1-year survival 52%.*

Conclusion: *The combination of oral capecitabine with i.v. oxaliplatin appears to be effective and well tolerated in patients with mCRC.*

Key words: capecitabine, chemotherapy, metastatic colorectal cancer, oxaliplatin

Introduction

CRC is the second most common malignancy in Europe after breast cancer in women and lung cancer in men [1]. Approximately 25% of patients present with metastatic disease. Despite improvements in adjuvant therapy, a substantial number of patients with localized disease will ultimately develop metastatic disease. The 5-year survival for patients with mCRC is less than 10% [1].

mCRC patients are often incurable and are given palliative chemotherapy in order to control symptoms, maintain or improve quality of life and prolong symptom-free and OS [2,3].

Palliative chemotherapy of mCRC has evolved dramatically over the past decades. While 5-FU initially was the mainstay of treatment in this setting, combinations with newer cytotoxic agents and also incorporation of novel targeted agents have yielded substantial improvements in the management of mCRC. Consequently, median OS may now approach 18-21 months [3-6].

The introduction of new therapeutic agents, such as oxaliplatin and capecitabine, has generated a variety of new therapeutic options in patients with mCRC, and this has resulted in positive effects on OS, PFS, and quality of life [7,8].

Multicentre phase I and II studies of combination chemotherapy with XELOX for advanced CRC have demonstrated remarkable response and survival rates with acceptable toxicity [9-11].

Capecitabine is highly active in patients with CRC [9-11]. Data from two large phase III trials have demonstrated that as first-line therapy for mCRC, capecitabine achieves significantly superior response rates (p

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<0.0002) and equivalent PFS and OS compared with i.v. bolus 5-FU-LV (Mayo Clinic regimen) [11-13].

Oxaliplatin is a third-generation cisplatin analog, with activity and toxicity profiles that differ from those of other platinum derivatives, including cisplatin and carboplatin [9,10]. Unlike other platinum compounds, oxaliplatin is active in colorectal cancer and had shown synergistic activity with 5-FU in preclinical studies [13,14].

The dose-limiting toxicity of oxaliplatin is neurotoxicity [9,10,12]. Neurotoxicity has two distinct manifestations: acute, transient symptoms are due to peripheral sensory and motor neuron hypersensitivity; and cumulative, persistent symptoms that are due to chronic peripheral sensory neuropathy [9,10]. The pathogenesis of acute neuropathy is thought to be attributable to a temporary dysfunction of an ion channel in the nerve membrane, while chronic sensory neuropathy may be a result of direct, cumulative neurotoxic effects resulting from platinum accumulation in the dorsal root ganglia [11,14,15].

As an oral fluoropyrimidine, capecitabine has the potential to replace i.v. 5-FU and simplify combination therapy. Like 5-FU, capecitabine may also have synergistic activity with oxaliplatin, and its tumor-selective activation and favorable safety profile could further improve the efficacy and safety of the combination [12,13].

Two randomized phase III trials demonstrated that, compared with 5-FU-LV alone, the addition of oxaliplatin to first-line 5-FU-LV therapy significantly increased objective response rates ($p < 0.001$) and median PFS ($p < 0.05$), with one trial [11] showing a trend towards superior OS, which, however, did not reach statistical significance [16].

The objectives in this study were to determine efficacy parameters, including PFS, OS, as well as safety.

Methods

Patients

mCRC patients were consecutively treated at the Department of Oncology of our hospital during 2005-2006.

Eligibilty criteria for this study included the following: histologically proven diagnosis of metastatic adenocarcinoma of the colon or rectum, life expectancy >3 months, Eastern Cooperative Oncology Group (ECOG) performance status score ≤2, normal blood cell count (neutrophil count $\geq 2.0 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, and serum hemoglobin concentration ≥10 g/dl), adequate liver function (biluribin serum level <1.25 upper limit of normal) and renal function (serum creatinine <1.25 upper limit of normal).

Exclusion criteria included the following: previous chemotherapy for metastatic disease, uncontrolled metabolic disorder or active infection, inflammatory bowel disease, severe cardiac disease and symptomatic cerebral metastasis.

Study objectives

The objectives of this phase II study were to determine: a) response rates; b) PFS; c) OS; and d) Toxicity profile.

Chemotherapy, dose modifications and toxicity

Oxaliplatin 130 mg/m^2 was infused over 2 hours on day 1, while capecitabine 2000 mg/m^2 was given in two divided doses on days 1-14. Cycle repetition was on day 21.

World Health Organization (WHO) grade 3 or 4 toxicity other than alopecia led to dose reduction or termination of treatment.

The dose of oxaliplatin and capecitabine was decreased by 25% in case of ≥3 hematological toxicity or paresthesias with pain and functional impairment lasting for > 7 days, or paresthesias with pain persisting between cycles. In case of grade 4 neutropenia or thrombocytopenia lasting >1 week, or febrile neutropenia, treatment was discontinued.

Response and survival assessment

Responses were estimated according to World Health Organization (WHO) response criteria. CR = dissapearance of all known lesions, PR = at least 50% decrease of the lesions, SD = neither PR nor PD, PD = 25% or more increase of the lesions or appearance of new lesions.

Full blood count, serum biochemistry, and imaging studies were assessed at baseline and after each chemotherapy course.

OS was measured from the day of entry until last follow up or death. PFS was measured from the first day of treatment to clinical or imaging tumor progression.

Statistical analysis

PFS and OS were determined using the Kaplan-Meier method. Analysis of differences between survival curves were assessed with the log-rank test. Statistical analyses were performed using the SAS software version 8.2 for Windows.

Results

Patient and disease characteristics are described in Table 1. Previous patients' treatment included surgery in 27 (79%) patients, adjuvant chemotherapy in 8 (23%), and radiotherapy in 4 (11%). A total of 182 cycles were administered (median 5, range 4-6 per patient).

No patient achieved CR. Fourteen (41%) patients showed PR, 9 (26%) SD, and 11 (32%) PD (Table 2). Median PFS was 5.5 months, median OS 12.9 months and 1-year survival 51% (Figures 1,2).

Grade 3 diarrhoea was seen in 16% of the patients. Hand-food syndrome (HFS) was seen in most patients; 6/34 (17%) with grade 1, 12/34 (35%) with grade 2 and 10/34 (29%) with grade 3 (Table 2). Other important toxicities included grade 3 neutropenia (23%), grade 3 nausea and vomiting (20%), and grade 3 peripheral neuropathy (11.7%; Table 3).

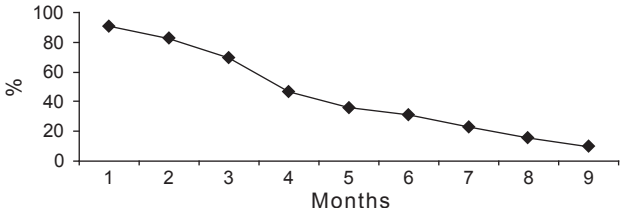

Figure 1. Progression-free survival.

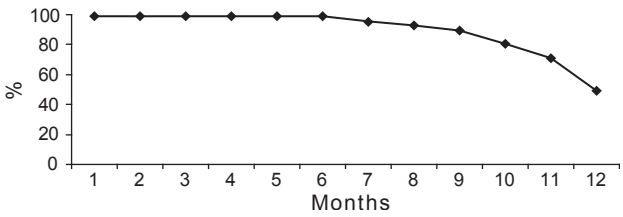

Figure 2. Overall survival.

Table 1. Patient characteristics

Characteristic	*n*	*%*
Age (years)		
Median	53.5	
Range	42-65	
Sex		
Males	23	67
Females	11	32
Performance status (ECOG)		
0-1	18	52
1-2	16	48
Histology		
Adenocarcinoma	34	100
Metastatic sites		
Liver	23	67
Lung	7	20
Bone	4	12

Table 2. Response to XELOX

	Patients n (%)		
	Liver	*Lung*	*Bone*
Complete response	–	–	–
Partial response	11 (32)	3 (8.8)	–
Stable disease	4 (11)	1 (3)	4 (11)
Progressive disease	8 (23)	3 (8.8)	–

Table 3. Non-hematologic and hematologic toxicities

Toxicity	*Grade n (%)*			
	1	*2*	*3*	*4*
Nausea-vomiting	15 (44)	8 (23)	7 (20)	–
Diarrhoea	8 (23)	7 (20)	6 (17)	–
Hand-foot syndrome	6 (17)	12 (35)	10 (29)	–
Neuropathy	16 (47)	14 (41)	4 (11.7)	–
Neutropenia	–	–	8 (23)	–
Anemia	6 (17)	–	–	–

Discussion

The standard chemotherapy regimen used as first-line treatment of colorectal cancer for many years was i.v. bolus 5-FU modulated by LV, but this has recently been superseded by newer combination regimens involving LV-modulated 5-FU given as a mixed bolus and continuous infusion with the addition of either oxaliplatin or irinotecan [6].

Capecitabine is an oral fluoropyrimidine that has established efficacy in the treatment of mCRC. Capecitabine and oxaliplatin in combination have been tested in a range of different administration schedules and doses with no evidence of major toxicities, and have demonstrated activity in mCRC.

Oxaliplatin, an organoplatinum complex, is usually classified as alkylating agent although it is not capable of actually adding alkyl groups to DNA. Oxaliplatin is an integral component of the various FOLFOX regimens, which have become a standard treatment for metastatic and node-positive colorectal cancer [3,4,17]. Encouraging results have been reported from phase II trials using oxaliplatin in combination with pemetrexed, raltitrexed or capecitabine in patients with mCRC [18]. The efficacy of oxaliplatin/5-FU/LV regimens has been tempered by the associated neurotoxicity which can significantly impair the quality of life of patients and limits the optimal use of oxalipla-

tin. Many published trials provide limited details concerning the precise type and location of neurotoxicities experienced, and most appear to have focused on the cumulative sensory neuropathy [16,17,19].

In a study that employed oxaliplatin 85 mg/m^2 given over 2 hours as first-line therapy for mCRC, the mean incidence of grade 3 or worse neuropathy was 15.4%. A higher incidence of grade 3 neuropathy (31-34%) was reported when oxaliplatin was given at 20 mg/m^2 as a 24-hour infusion daily for 5 days every 3 weeks or as 100 mg/m^2 over 2 hours every 2 weeks [20].

In patients who receive more than 6 cycles of chemotherapy (projected maximum cumulative dose in this every 3-week schedule of 780 mg/m^2), neuropathy can become persistent and affect the subject's ability to perform routine activities of daily living. Oxaliplatin-associated cumulative sensory neuropathy is slowly reversible in most patients [9,10].

There is no standard treatment for oxaliplatin-related neurotoxicity. A variety of strategies have been employed to prevent or treat oxaliplatin neurotoxicity including carbamazepine, gabapentin, alpha lipoic acid, amifostine, glutathione, and celecoxib [10,16,17].

Our study demonstrated that most patients experienced either dysesthesia or paresthesia at some point during their treatment, although the worst toxicity was grade 1 in most patients (n=16).

In a phase II study of first-line capecitabine and oxaliplatin therapy of advanced CRC in 96 patients, response rates were 60 vs. 53% in patients less than 60 years of age vs. elderly (p=0.51) [9].

The use of oxaliplatin is increasing and has resulted in significant improvements in outcomes in CRC. However, although acute peripheral sensory or motor nerve hyperexcitability seem to be trancient in nature, oxaliplatin-associated neurotoxicity can cause detrimental effects to the patient's quality of life and may require dose reduction or drug discontinuation. Our study provides detailed information on the incidence, type and duration of oxaliplatin neurotoxicity. Further understanding of oxaliplatin-associated neurotoxicity is necessary to warn patients of potential side effects and to facilitate strategies to prevent or treat neurotoxicity. Optimizing the quality of life of cancer patients is of paramount importance. Continued research on oxaliplatin will help achieve this goal while also providing further progress with respect to clinical benefit outcomes.

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