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ORIGINAL ARTICLE

Biweekly oxaliplatin plus 1-day infusional fluorouracil/leucovorin followed by metronomic chemotherapy with tegafur/uracil in pretreated metastatic colorectal cancer

Peng-Chan Lin · Wei-Shone Chen · Ta-Chung Chao · Shung-Haur Yang · Chui-Mei Tiu · Jin-Hwang Liu

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Abstract
Purpose Metronomic chemotherapy, at a minimally toxic dose and with a frequent schedule, is a potentially novel approach to the control of advanced cancer disease via a different mechanism from maximum tolerable doses chemotherapy. Taking advantage of the potential effectiveness of metronomic therapy, tegafur/uracil (UFT) was incorporated into an oxaliplation/infusioanl fluouracil (5-FU)/leucovorin (LV) protocol in this study. The primary endpoints were response rate, time to progression (TTP) and safety profile in 5-FU-pretreated metastatic colorectal cancers (CRCs).
Patients and methods Twenty-eight patients with metastatic CRCs resistant or refractory to 5-FU/LV were enrolled. Chemotherapy was administrated every 2 weeks sequentially with 2-h infusion of oxaliplatin (85 mg/m^2) and LV (200 mg/m^2), intravenous bolus 5-FU (400 mg/m^2), 22-h infusion of 5-FU (600 mg/m^2) on day 1 and then followed by 10-day daily oral UFT (200 mg/m^2)/LV (30 mg/m^2).
Results Partial response was seen in ten (35.7%) patients. The median TTP was 5.2 (95% CI: 4.16–6.31) months and the median overall survival was 13.4 (95% CI: 6.39–20.5) months. No grade 3 toxicities above 5% according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) occurred except sensory neuropathy (10.7%). No grade 4 toxicity, treatment-related mortality or hand–foot syndrome was found.
Conclusions This study protocol with favorable toxicity profile is thus promisingly effective against 5-FU-pretreated metastatic CRCs. Given the present experience, an evaluation of the regimen as front-line treatment of metastatic CRC is planned.

Keywords Colorectal cancer · Tegafur · UFT · Oxaliplatin · Metronomic chemotherapy

P.-C. Lin · T.-C. Chao · J.-H. Liu (✉)
Division of Medical Oncology, Taipei Veterans General Hospital and National Yang-Ming University,
No. 201, Shi-Pai Rd., Sec. 2, Taipei 112, Taiwan, ROC
e-mail: jhliu@vghtpe.gov.tw

P.-C. Lin
Division of Hematology and Oncology,
Department of Medicine, College of Medicine,
National Cheng Kung University Hospital,
Tainan, Taiwan, ROC

W.-S. Chen
Division of Experimental Surgery,
Taipei Veterans General Hospital,
School of Medicine National Yang-Ming University,
Taipei, Taiwan, ROC

W.-S. Chen · S.-H. Yang
Division of Colorectal Surgery,
Taipei Veterans General Hospital,
School of Medicine National Yang-Ming University,
Taipei, Taiwan, ROC

C.-M. Tiu
Department of Radiology,
Taipei Veterans General Hospital,
School of Medicine National Yang-Ming University,
Taipei, Taiwan, ROC

Introduction

Chemotherapy with doublet containing either oxaliplatin or irinotecan and fluouracil (5-FU)/leucovorin (LV) has nearly become standard for metastatic colorectal cancers (CRCs), both in front line and in after

5-FU/LV therapies [1–7]. Nonetheless, metastatic CRC is rarely cured even using combination modalities and new effective drugs. Therefore, decreasing the treatment toxicities and administration convenience are often desired while a high response efficacy is pursued.

Antiangiogenic treatment is one modalities widely used recently for cancer therapy. Effects of antiangiogenic treatment can be achieved by angiogenesis inhibitors of which one successful example is the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab (Avastin; Genentech, South San Francisco, CA) [8]. In an alternative way, tumor endothelial cells are also sensitive to the action of conventional cytotoxic drugs, if the dosing regimen is modified. The concept, known as antiangiogenic scheduling or metronomic chemotherapy, was demonstrated in preclinical studies using transplanted tumor models [9–12]. Metronomic chemotherapy, administrated chronically at relatively low, minimally toxic doses on a frequent schedule at close regular intervals without prolonged drug-free breaks, is reported to be potentially able to control advanced cancer disease at significantly reduced undesirable toxic side effects [13, 14]. Integrating metronomic chemotherapy into treatment course at appropriate time point is thus reasonable for treatment of metastatic CRCs.

Tegafur/uracil (UFT) is one of the effective chemotherapeutics reported to be an effective antiangiogenic agent in an animal model of metastatic CRCs and postoperative non-small cell lung cancer patients [15, 16]. UFT is a combination of tegafur and uracil at a molar ratio of 1:4, where tegafur is an orally bioavailable prodrug of 5-FU [17, 18]. Uracil herein reversibly inhibits the primary catabolic enzyme, dihydropyrimidine dehydrogenase, involved in degradation of 5-FU and thus offers pharmacokinetic modulation of 5-FU. UFT is thus a promising metronomic chemotherapeutic for metastatic CRCs.

Oxaliplatin plays a key role in pretreated metastatic CRCs; however, 5-FU was not dispensable because the response rate (RR) of monotherapy using oxaliplatin was only 10% in pretreated metastatic CRCs [19]. Clinically, oral cytotoxic UFT (300 or 350 mg/m^2/day)/LV (75 or 90 mg/day) chemotherapy for metastatic CRCs in randomized comparative studies has shown to be as effective as intravenous 5-FU/ LV in overall survival (OS), time to progression (TTP) or tumor response with substantial safety and low cost [20–23]. Feliu et al. [24] reported that UFT plus oxaliplatin is an active chemotherapy regimen with 35% overall RR, a median TTP of 7.3 months and a median OS of 16.8 months in previous untreated advanced CRC patients. Notwithstanding, in a phase II study, oxaliplatin plus cytotoxic UFT/LV alone for pretreated metastatic CRCs showed RR of 12.9% (95% CI: 3.6–29.8%) and median TTP of 9 weeks and OS of 26 weeks and suggested not as effective as other oxaliplatin and infusional 5-FU/LV doublets [25]. Therefore, further modification of 5-FU/UFT administration schedules in oxaliplatin-containing regimens may be attempted to decrease toxicities without compromising the treatment efficacy.

In this study, we tested the efficacy and toxicities of oxaliplatin plus 1-day infusional 5-FU/LV followed by metronomic UFT with less than maximum tolerable dose intensity in the oxaliplatin-containing regimen for pretreated metastatic CRC patients.

Patients and methods

Eligibility

The protocol was approved according to the institutional guideline and informed consent was obtained from each patient before enrollment. Eligibility criteria included colorectal carcinoma proven histologically and metastatic lesions measured at a minimum of 2 cm × 2 cm. All of the patients had failed intravenous 5-FU/LV and had documented recurrence or progression of the disease. Patients with brain metastasis and secondary primary cancer were excluded from this study. Other eligibility criteria were age ≥ 21 years and Eastern Cooperation Oncology Group (ECOG) performance status ≤2. Clinical, biological and radiological assessments were performed within 7 days before the start of treatment. Adequate bone marrow, renal and hepatic functions were required (absolute neutrophil count [ANC] $\geq 1.5 \times 10^9\,l^{-1}$, platelet count $\geq 100 \times 10^9\,l^{-1}$, bilirubin ≤2.0 mg/dl, serum alanine transaminase and aspartate transaminase levels not greater than three times the upper normal levels, and creatinine <2.0 mg/dl) prior to each cycle of treatment.

Chemotherapy regimen and dose modification

Chemotherapy regimen consisted of biweekly 2-h intravenous infusion of oxaliplatin (at 85 mg/m^2) and LV (200 mg/m^2), followed sequentially by intravenous 5-FU bolus (400 mg/m^2), 22-h 5-FU infusion (600 mg/m^2) on day 1 and then 10-days' daily oral UFT (200 mg/m^2, in three divided doses)/LV (30 mg/m^2) (days 2–11). Toxicities were evaluated according to the NCI-CTC, version 3.0. Following the initial treatment protocol, for cycles resulting paresthesias/dysesthesias of grade 3

for longer than 1 week or grade 2 longer than 2 weeks, oxaliplatin was withheld until symptom resolution and decreased to a dose of 65 mg/m^2 for subsequent cycles; if the above neurological symptoms recurred, oxaliplatin was again withheld until symptom resolution and decreased further to 50 mg/m^2. Oxaliplatin was discontinued if the above symptoms recurred after two dose reductions, paresthesias/dysesthesias of grade 3 once persisted for longer than 2 weeks or dose delay over 2 weeks due to toxicity.

For grade 3 hematological toxicities, subsequent chemotherapy was withheld till recovery and infusional 5-FU/LV was decreased to 80% of the protocol dosage. Study was discontinued if grade 3 toxicities recurred after dose decrease, dose delay over 2 weeks due to toxicity or grade 4 toxicity occurred.

Treatment assessment

Before treatment, a full medical history was obtained for each patient and each patient underwent a performance status assessment and physical and laboratory examinations. Measurable lesions were assessed using computerized tomography or magnetic resonance imaging. Patients underwent electrocardiography, chest X-ray, complete hemogram, blood chemistry, carcinoembryonic antigen (CEA), and urinalysis. Visible or palpable lesions were also measured. Assessment of measurable lesions was repeated every four cycles, or earlier in case of clinical deterioration. Treatment was discontinued when the disease progressed or when toxicities occurred as specified. Objective responses were recorded according to Response Evaluation Criteria in Solid Tumors (RECIST) and responses were confirmed at least 4 weeks later [26].

Statistical analysis

Patients who received at least two cycles of treatment were assessable for response unless they had definitive evidence of progression after the first cycle. They were then categorized as having progressive disease. Patients who had at least one cycle of treatment were assessable for toxicities. TTP was defined as the time from study entry to documented disease progression. OS was measured from the day of entry until last follow-up or death. Actuarial survival was estimated by the Kaplan–Meier method. The trial was designed as a phase II study, with RR as well as toxicity profile as the main end point. The reported RRs of oxaliplatin/5-FU/LV combination therapies for 5-FU-pretreated patients with advanced CRCs are between 20 and 46%, with a median of 34% [4–8]. Simon's two-stage design was applied to calculate the sample size [27]. With a sample size of 33, our study had 80% power to accept the hypothesis that the true RR was greater than 40%, and 5% significance to reject the hypothesis that the true RR was less than 20%, if there were 10 or more responses. At the first stage, if there were fewer than four responses from the initial 18 patients, this study would conclude that the anticipated RR was less than 20% and the study would be terminated. The significance of risk factors for predicting the response was examined by a test of association using chi-square values from a 2×2 table. All analyses were performed using the Statistical Package for Social Sciences, version 11.0 (Chicago, IL) for Windows.

Results

Patients and treatment

From January 2001 to December 2004, 28 patients with metastatic CRC refractory or resistant to 5-FU were enrolled in the study. All patients were assessable for response, survival, and toxicities. There were six responses among the initial 18 patients so that more patients enrolled were continued to achieve the goal of ten responses among 33 patients. Ten responses had been established after 28 patients and the enrollment terminated. Only the rare patients could have been enrolled for oxaliplation or irinotecan-containing doublet therapies had become the standard front line treatment for metastastic CRC in the end of enrollment. The cut-off date of follow-up for TTP and OS were June 30, 2006, with a median potential follow-up time for the entire cohort of 14.9 months. The age ranges from 33 to 82 with median of 68. Seventeen patients had primary cancer at colon and 11, at rectum. Fourteen patients had metastases to liver; 11, to lungs and 14, to other organs. Patients' characteristics probably affecting prognosis as reported elsewhere were listed in Table 1. Twenty-eight patients registered and all were assessable for response, survival and toxicities. The median cycle number of chemotherapy was seven. For the first four cycles of chemotherapy, the relative dose intensity of oxaliplatin was 0.82; so were the relative dose intensity of 5-FU and UFT. All 28 patients had been treated with infusional LV5FU2 regimen [28] and eventually became resistant or refractory before entry. After disease progressed from this oxaliplatin/5-FU/LV/UFT study protocol, 18 (64.3%) patients received further chemotherapy with irinotecan-containing regimen and none of them has ever received target therapy agents such as cetuximab or bevacizumab.

Table 1 Patient characteristics and stratification with risk factors

Risk factors	Number of patients (%)	Number of responders	*P* values
Performance status			
0	9 (32.1)		
1	12 (42.8)	11	0.008
2	7 (26.9)	1	
Number of organs involved			
1	19 (67.8)	8	0.059
≥2	9 (32.1)	4	
Alkaline phosphatase			
<1.5 normal upper limit	24 (85.7)	11	
≥1.5 normal upper limit	4 (14.3)	1	<0.001
CEA			
Normal	7 (15.0)		
Increased > 5 ng/ml	13 (46.4)	9	0.023
Increased ≥100 ng/ml	8 (28.6)	3	
Maximum tumor Sectional area			
≤25 cm^2	21 (75.0)	9	0.008
>25 cm^2	7 (25.0)	3	

Efficacy

Efficacy in terms of RR, TTP, and OS were analyzed for all registered patients. Safety assessments were also performed. The objective RR was 35.7% (10/28) (95% CI: 23.3–62.3), with 10 PRs and no CR. TTP and OS curves are shown in Fig. 1 with a median TTP of 5.2 (95% CI: 4.16–6.31) months and a median OS of 13.4 (95% CI: 6.39–20.5) months.

Response according to clinical variables

The patients' characters were listed in Table 1 and stratified by the five risk factors: (a) ≥2 of ECOG performance status (PS), (b) metastases to two or more organs, (c) >1.5-fold upper normal limit of alkaline phosphate, (d) >100 ng/ml of CEA level, and (e) >25 cm^2 (product of two perpendicular diameters) for maximum tumor sectional area, which were reported to be predictive of poorer OS in 5-FU-resistant or refractory CRC patients treated with oxaliplatin/5-FU/LV [6]. All of them significantly predict poorer response except metastases to two or more organs, which is borderline significant to predict response.

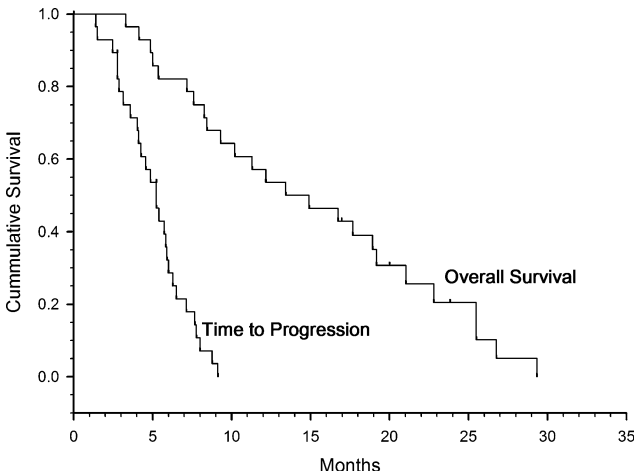

Fig. 1 Kaplan–Meier curves of overall survival (OS) and time to progression (TTP) for 28 patients

Toxicities

The 28 patients received a total of 165 courses of chemotherapy and all were assessable for toxicities. Grade 3 toxicities per patient were listed in Table 2. Grades 3 toxicities happened as anemia, leukopenia, vomiting and sensory neuropathy; however, none exceeded 5% except sensory neuropathy (10.7%). No hand–foot syndrome, leucopenic fever, any grade 4 toxicities or treatment-related mortalities occurred in this study.

Table 2 Incidence of toxic effects (%) per patient

Toxic symptoms any (Grades 1–4)[a]	Number of patients (%)
Anemia	
Any	24 (85.7)
Grade 3	1 (3.6)
Leukopenia	
Any	13 (46.4)
Grade 3	1 (3.6)
Thrombocytopenia	
Any	6 (21.4)
Grade 3	0 (0)
Nausea	
Any	21 (75.0)
Grade 3	0 (0)
Vomiting	
Any	18 (64.3)
Grade 3	1 (3.6)
Diarrhea	
Any	7 (25.0)
Grade 3	0 (0)
Liver	
Any	1 (3.6)
Grade 3	0 (0)
Stomatitis	
Any	5 (17.8)
Grade 3	0 (0)
Sensory neuropathy	
Any	24 (85.7)
Grade 3	3 (10.7)
Hand–foot syndrome	
Any	0 (0)

NS not significant ($P \geq 0.05$)

[a] No grade 4 toxicity was recorded

Discussion

In view of a survival benefit in metastatic CRCs from antiangiogentic treatment, metronomic chemotherapy with a probable antiangiogenic effect added to oxaliplatin/ infusional 5-FU/LV would be promisingly effective [29]. The RRs of oxaliplatin/5-FU/LV combination therapies for 5-FU-pretreated patients with advanced CRC are between 20 and 46% with a median of 34% [3–6]. Our study has thus demonstrated that integrating metronomic UFT/LV into oxaliplatin plus 1-day infusional 5-FU/LV is promisingly effective against 5-FU-pretreated metastatic CRCs. Furthermore, the median TTP and OS of this studied protocol were not deviated from the reported range of doublet containing oxaliplatin and infusional 5-FU/LV for pretreated metastatic CRCs [2–6]. Comparing the patients' demography by the prognostic factors in our study to those in trials of oxaliplatin and infusional 5-FU/LV for pretreated CRCs, patients in this study did not show a significantly favorable profile [6].

In addition to contribution from oxaliplatin and a probable antiangiogenic effect from metronomic UFT chemotherapy as discussed above, another probable underlying mechanism to make this study protocol effective is the dual cytotoxicity mechanisms of 5-FU. As observed in WiDr colon cancer cell line, exposure to oxaliplatin and 5-FU/LV according to clinically relevant LV5FU2 schedule led to G1-S arrest and apoptosis [30], we may thus expect similar events occurred when patients were treated with oxaliplatin and infusional 5-FU/LV in our study protocol. The following metronomic chemotherapy with prolonged UFT at less than usually cytotoxic dose (daily 200 mg/m^2 vs. daily 300–350 mg/m^2 [19, 20]) may lead to G2-M cell cycle arrest and mitotic catastrophe as CRC cells exposing to 5-FU at a much low plasma concentration [31, 32].

As reported previously, the dose-limiting toxicities for the biweekly oxaliplatin/infusional 5-FU/LV therapy in metastatic CRCs were leukopenia and cumulative neurosensory toxicity [4, 6]. In this study, grades 3 leukopenia was significantly decreased to less than 5% per patient and no grade 4 toxicity was found. Other non-neurological toxicities were also rare and less than 5%. Since grades 3 and 4 leukopenic and anemic toxicities for oxaliplatin/infusional 5-FU/LV were usually above 10 and 5%, respectively [4, 6], non-neurological toxicities in this study is relatively low and well acceptable. Grade 3 sensory neuropathy, which happened in 10.7% of patients, seemed to be as high as reported in those treated with other oxaliplatin/infusional 5-FU/LV protocols having reported and is deemed due to oxaliplatin. Besides, no hand–foot syndrome occurred as not unusually in patients treated with capecitabine; neither bleeding or hypertension occurred as occasionally in those treated with bevacizumab treatment was found [28].

We conclude that oxaliplatin plus infusional 5-FU/LV followed by metronomic UFT is an active regimen with low-toxicity and low cost for 5-FU refractory and resistant patients. Further study to evaluate this regimen as front-line treatment of metastatic CRC is warranted.

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