Original Article

Oxaliplatin/5-Fluorouracil/Leucovorin (FOLFOX4) in Metastatic Colorectal Cancer (CRC)

Cheng-Jen Ma[1]
Jan-Sing Hsieh[1,2]
Fang-Ming Chen[1,2]
Hon-Man Chen[1,2]
Che-Jen Huang[1,2]
Tsung-Jen Huang[1,2]
Jaw-Yuan Wang[1,2]
[1]*Department of Surgery, Kaohsiung Medical University Hospital,*
[2]*Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

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Purpose. In studies of Western countries, oxaliplatin/5-fluorouracil/ leucovorin (FOLFOX4) has been shown to be an effective and well-tolerated regimen for patients with metastatic colorectal cancer. However, the toxicity profile and efficacy of FOLFOX4 in the Taiwanese population may be different from that of Caucasians. This study evaluates the toxicities of FOLFOX4 and the objective response rate achieved in our patients with metastatic colorectal cancer.
Methods. Forty patients with metastatic colorectal cancer managed with FOLFOX4 between January 2005 and April 2006 in Kaohsiung Medical University Hospital were analyzed retrospectively. Toxicities were regularly recorded by the National Cancer Institute common toxicity system and tumor responses were assessed radiologically with a computed tomographic (CT) scan every four cycles, according to the Response Evaluation Criteria in Solid Tumors (RECIST).
Results. Of all toxicities recorded, grade 1 hypersensitivity was found with a rate of 20% (8/40). The rate of sensory neuropathy encountered was 40% (16/40), mainly grade 2 (11/40). Among 16 patients with neuropathy, two (5%) had grade 3 paresthesia, which did not resolve after FOLFOX4 had been discontinued for over half-a-year. There was no pharyngo-laryngeal dysesthesia observed. Gastrointestinal adverse effects were mild to moderate and few of them needed intravenous hydration therapy. The overall response rate (all partial responses) was 45% (18/40) and the stable disease rate was 20% (8/40). Six patients (15%) died in the therapeutic period but none of their deaths was due to toxicities.
Conclusions. FOLFOX4 is a favorable effective regimen coupled with an acceptable safety profile for metastatic colorectal cancer among Taiwanese. [*J Soc Colon Rectal Surgeon* (*Taiwan*) *2007;18:65-72*]

Colorectal cancer (CRC) is the second leading cause of cancer-related mortality in Europe and the USA, and approximately 300,000 new cases and 200,000 deaths due to CRC are reported in these areas annually.[1] In Taiwan, CRC is the third most frequent occurring malignancy and the third major cause of cancer-related death among all cancers. There are over 7000 new cases and 3000 deaths per year (http:// www.doh.gov.tw/statistic/index.htm; accessed in October 2006). The incidence of colorectal cancer in Taiwan was 35.06/100,000 in 2002, gradually approaching Western figures in recent decades.
5-Fluorouracil/Leucovorin (5-FU/LV)-based regimens are recommended as the first-line chemotherapy for patients with colorectal cancer in the United States and Europe.[2-3] Adjuvant postoperative treatment with 5-FU/LV in curatively resected stage III colon cancer significantly

reduces the risk of cancer recurrence and improves survival.[4] There was a reduction of recurrence from 56% to 39% and a reduction of death from 51% to 40% for stage Dukes' C CRC after more than five years of follow-up.[5] In the last few years, with the introduction of novel drugs, the options of treatment for patients affected by advanced CRC have considerably increased. Oxaliplatin is a third-generation platinum derivative, which, when combined with 5-FU/LV has led to a significant improvement in median survival compared with 5-FU/LV alone in patients with metastatic diseases.[6-8] Studies in the USA show that for patients with metastatic CRC, palliative chemotherapy has resulted in prolonged survival and improved quality of life.[9] The European experience with oxaliplatin has also shown an acceptable toxicity profile.[6-8] However, the toxicity profile and the efficacy of oxaliplatin/5- fluorouracil/leucovorin (FOLFOX4) has resulted from clinical trials conducted in Western countries, mainly on Caucasians, and this may be different for Taiwanese.

Herein, we report the experience with FOLFOX4 among our patients with metastatic CRC, focus on the toxicities encountered, and the objective response rate obtained.

Methods

We conducted a retrospective analysis from January 2005 to April 2006 of patients with histologically confirmed metastatic CRC at the Department of Surgery, Kaohsiung Medical University Hospital. Initial staging work-up included history and physical examination, routine biochemistry, blood cell count, carcinoembryonic antigen (CEA) serum level determination, chest X-ray and abdominal computed tomographic (CT) scan. Magnetic resonance (MRI), bone scan, or positron emission tomography (PET) would be necessary if specific site of metastases was suspected. Eligibility criteria included inoperable metastatic histologically-confirmed CRC, a measurable disease, which is defined as the presence of at least one lesion larger than 2 cm evaluated by images. In total, there were 40 metastatic CRC patients with measurable and evaluated lesions that were enrolled into this study. Our primary objectives were to assess the toxicities and the efficacy of FOLFOX4. The following characteristics of patients were recorded: age, gender, performance status, location of primary tumor, time and site of metastases, and previous chemotherapy. FOLFOX4 was conducted comprising oxaliplatin 85 mg/m^2 as a two-hour infusion on day 1, LV 200 mg/m^2 as a two-hour infusion concurrently with oxaliplatin on day 1, followed by a bolus of 5-FU 400 mg/m^2 then, and continuous infusion of 5-FU 600 mg/m^2 over 22 hours. Courses were repeated every two weeks in the presence of an absolute neutrophil count =1500/μ l and platelet count ≥ 100000/μ l, and recovery of any extra-haematological toxicity; otherwise, treatment was postponed for one or two weeks until recovery. Also, the chemotherapy was continued until the disease progressed or unacceptable toxicities developed or the patient refused further treatment with FOLFOX4.

Toxicity was evaluated based on the National Cancer Institute common toxicity criteria grading system (http://ctep.cancer.gov/reporting/ctc.html; accessed in October 2006). Patient response was assessed radiologically every four cycles with a CT scan and the best response was recorded. Responses were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST).[10] A complete response was defined as the disappearance of all target lesions; a partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as a reference point the baseline sum's longest diameter; progressive disease was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as a reference the smallest sum of longest diameters recorded since the treatment started or the appearance of one or more new lesions; a stable disease was defined as neither having sufficient shrinkage to qualify for a partial response nor a sufficient increase to qualify for progressive disease, taking as reference the smallest sum of the longest diameters since the treatment started. The time for the first response assessment was usually after the fourth cycle. Response reassessments were typically performed after the eighth or twelfth cycles. We report the best response which is defined as the best response recorded by the investigators, since the

confirmatory radiological evidence of response after four weeks was not consistently available.

Results

A total of 40 patients with metastatic CRC were analyzed retrospectively and their characteristics have been summarized in Table 1. There were 23 males and 17 females with a median age of 62 years old (range 32-82). The majority (95%) of patients had a good initial performance status (Eastern Cooperative Oncology Group [ECOG] performance status grading system 0-1) before FOLFOX4 was conducted. Among these patients, 80% of the primary tumors were located in the colon and 20% in the rectum with 27.5% of synchronous metastases, and the rest subsequently developed metastatic disease dup to adjuvant therapy. The main site of metastases was the liver (45%), followed by local recurrence (22.5%), lung (17.5%), distant lymph node (5%), and bone (2.5%) consecutively. Thirty percent of the patients had metastases in more than one site. The total cycles of chemotherapy administered were 384, with a median of ten cycles per patient (range 2-18). Out of 40 patients, 34 (85%) patients were identified as having abnormal pre-operative serum CEA levels.

The toxicities encountered are listed in Table 2. A grade 3 hypersensitivity reaction (anaphylactic-like) was not found and grade 1 hypersensitivity (transient skin rash and drug fever $< 38^{o}C$) was encountered in eight (20%) patients, but no therapies were aborted consequently. Intravenous administration of an antihistamine, with or without steroids, alleviated this side effect. There were two patients (5%) who experienced grade 1 neurosensory toxicity (loss of deep tendon reflexes or paresthesia [including tingling] but not interfering with function); and eleven patients (27.5%) experienced grade 2 toxicity (objective sensory loss or paresthesia [including tingling], interfering with function, but not interfering with activities or daily living). Only two patients (5%) had grade 3 neurosensory toxicity (sensory loss or paresthesia interfering with activities or daily living) that was recorded. However, these two patients were submitted to further cycles at reduced doses. All neurosensory toxicity developed during cycles 2-9 (median 5). No pharyngo-laryngeal dysesthesia was observed.

Neutropenia affected 15 (37.5%) patients. Severe neutropenia (grades 3 and 4) was observed in four (10%) patients and granulocyte-colony stimulating factors (G-CSF) was administered as a result. In any case, neutropenia was usually short-lived and was rarely complicated. The gastrointestinal presentations, including anorexia, nausea, vomiting, constipation, and diarrhea were mild, though 12.5% of the patients had complaints of grade 3 diarrhea, 2.5% had grade 3 nausea, 5% had grade 3 vomiting, and 5% had grade 3 stomatitis, which could be released by antidiarrheal, antiemetic agents and intravenous hydration, and none required therapy to be discontinued. It seems that there was no correlation between the initial performance status and toxicities that could be identified. The one patient with an ECOG performance status of two did not encounter grade 3 or 4 toxicities and the regimen went on. There were six patients who died in the period of the study, but no patient died from toxicities of FOLFOX4.

The objective responses of patients are summarized in Table 3. Among the 40 patients, eighteen had partial responses (PR) (Fig. 1a, b and Fig. 2a, b) but no complete responses were achieved, giving an overall response rate of 45%. The response rate reached 52% (14/27) and 36% (4/11) among those who underwent FOLFOX4 as the first-line and second-line chemotherapy, respectively. Of the 18 responders, 78% (14/18) of patients had FOLFOX4 as their first-line chemotherapy, and 56% (10/18) had liver-only metastases. When using FOLFOX4 as the third-line chemotherapy, no response was observed in our analyses. The incidence of stable disease (SD) was achieved in 20% (eight patients) at the same time. The overall disease control rate (PR+SD) was 65%. Most (64%) of the patients with progressive disease had multiple sites of metastases.

Discussion

Oxaliplatin is a third-generation platinum agent indicated for the treatment of CRC. The cytotoxic lesion of platinating agents is thought to be the platinum intra-strand crosslink that forms on DNA,

although treatment activates a number of signal transduction pathways.[11] Oxaliplatin has a non-hydrolyzable diaminocyclohexane (DACH) carrier ligand which is maintained in the final cytotoxic metabolites of the drug. Oxaliplatin in combination with 5-FU and LV, has been approved worldwide as a second-line treatment of metastatic CRC.

Oxaliplatin has a unique pattern of side effects and besides neurotoxicity, they include hematologic toxicity and gastrointestinal tract toxicity. Hypersensitivity reactions have been reported to occur after multiple cycles of therapy (range 2-17), with variable and unpredictable clinical features.[12] The reported incidence of hypersensitivity reactions associated with oxaliplatin in patients with CRC is approximately 12-16% in the Western population, with 1-2% of patients developing grade 3 or 4 in severity.[6,12,13] In our study, eight out of 40 patients (20%) experienced grade 1 hypersensitivity without fatal bronchospasm, allergy-related edema, angioedema or shock. All hypersensitivities could be managed well with intravenous steroids and antihistamine, and no treatment needed to be discontinued. Though no severe hypersensitivity was reported in our investigation, it was estimated to occur in about 1.32% of patients by another Taiwanese research team.[14] In such cases, initiation of a desensitization program successfully prevents further reactions and allows therapy with oxaliplatin to continue.[15] A literature review (1980-October 2006) showed that the most severe hypersensitivity reactions to oxaliplatin among Asians occurred among those of Chinese descent.[16]

Oxaliplatin neuropathy has a wide spectrum, ranging from an acute sensory neuropathy immediately following treatment to a chronic, cumulative dose-limiting neuropathy that usually takes several weeks of treatment to appear, and usually resolves several months after discontinuation of oxaliplatin. The cumulative neuropathy caused by oxaliplatin occurs in approximately 13-18% of patients, interfering with its function.[6,18] In the present study, only two patients (5%) encountered grade 3 paresthesia, which did not interrupt treatment, and no dose reduction was adapted since the neuropathy was acceptable to the patient. For one patient, the sensory neuropathy lasted for 28 weeks, and the other lasted for 54 weeks after cessation of oxaliplatin. The incidence of grade 3 neurotoxicity was similar to that of another Asian group studied[18]. De Gramont et al. reported that reversibility of grade 3 sensory neurotoxicity was observed in 74% of patients, and the median time to recovery from grade 3 neurotoxicity was 13 weeks.[6] In general, one-third of our patients experienced mild to moderate paresthesia. Furthermore, no pharyngo--laryngeal dysesthesia was observed, unlike in Western studies.

Consistent with observations from Goldberg et al.[8] and Giacchetti et al.,[17] a low percentage of patients with severe neutropenia (grades 3 and 4) were found in our investigation. G-CSF was administered and the problem of neutropenia was controlled, and then all the treatment could be carried on. Nausea and vomiting was usually mild to moderate and was readily controlled with standard antiemetics. The majority of the patients developed mild to moderate gastrointestinal toxicities, and the rate and the severity was lower than in previous reports.[6-9,17] No patients declined further FOLFOX4 treatment because of the toxicities encountered.

FOLFOX4 achieved an overall response rate of 45%, despite all being partial responses. It was administered in 52% of our patients as first-line chemotherapy and in 36% as second-line chemotherapy. This is comparable to the rate of its administration in Western studies, where it is given to 50% as first-line and 20-45% as second-line therapy.[6-8,17,19] In addition, 20% of our patients had a stable disease, and the overall disease control rate approximated 65%.

In conclusion, toxicities of FOLFOX4 we encountered were different from those in Western studies. There were similar incidences of hypersensitivity, but with no occurrence of life-threatening bronchospasm, angioedema or shock, lower percentage of grade 3 paresthesia and no pharygo-laryngeal dysesthesia, and lower rate and severity of gastrointestinal toxicities. However, the objective response was comparable to Western studies. Consequently, we suggest that FOLFOX4 is an effective regimen and a feasible chemotherapy with acceptable toxicities for our Taiwanese population with metastatic CRC.

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