Original Article

Efficacy and Safety of Weekly and Biweekly Cetuximab-Combined FOLFIRI Regimen as First-line Setting in Patients with Metastatic Colorectal Cancer: Experience in a Southern Taiwan Medical Center

Yung-Sung Yeh[1,2]
Cheng-Ying Chiang[1]
Chin-Fan Chen[1]
Cheng-Jen Ma[1]
Fang-Ming Chen[1,3]
Hon-Man Chan[1,3]
Che-Jen Huang[1,3]
Jan-Sing Hsieh[1,3]
Jaw-Yuan Wang[1,3]
[1]*Division of Gastroenterological Surgery, Department of Surgery*
[2]*Division of Trauma, Department of Emergency Medicine, Kaohsiung Medical University Hospital*
[3]*Department of Surgery, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Key Words
Biweekly;
Cetuximab;
Metastatic colorectal cancer;
Safety;
Efficacy

Purpose. This retrospective study was designed to analyze the two different regimens of weekly and biweekly cetuximab-combination FOLFIRI chemotherapy, and determine the toxicities and the efficacy of these two different regimens administered in Taiwanese patients with metastatic colorectal cancer (mCRC).
Methods. From January 2005 through December 2008, a total of sixty patients with metastatic colorectal cancer receiving target therapy of cetuximab-combination FOLFIRI chemotherapy were analyzed retrospectively. These patients were divided into two groups with different regimens of administration. In Group A, 26 patients received intravenous (IV) cetuximab weekly (400 mg/m^2 as a 120-min IV infusion at first week, then 250 mg/m^2 as a 60-min IV per week). In group B, 34 patients received intravenous (IV) cetuximab biweekly (500 mg/m^2 as a 120-min IV infusion per two-week). According to the Response Evaluation Criteria in Solid Tumor (RECIST), characteristics of each patient, toxicities, efficacy or tumor response were regularly recorded.
Results. The overall disease control rate (complete response + partial response + stable disease) was comparable of 76.8% (20/26) for group A and 82.4% (28/34) for group B respectively (p = 0.602). The progression-free survival was comparable between these two treatments (12 months in group A *vs.* 13 months in group B; p = 0.662). The efficacy of the every-2-weeks regimen was similar to the approved weekly dosing regimen. Among all recorded side effects, the incidence of grade 3 or 4 diarrhea was 11.5% (3/26) in group A and 8.8% (3/34) in group B. Grade 3 skin rash was seen in 3 patients (11.5%) from group A and 5 patients (14.7%) from group B. The incidence of grade 3 or 4 neutropenia /anemia/ thrombocytopenia encountered was 11.5% (3/26)/7.7% (2/26)/7.7% (2/26) in group A and 14.7% (5/34)/5.9%/ (2/34)/5.9% (2.34) in group B. There was no significant difference between these two different regimens of administration and all toxicities were easily controlled with standard therapies. No treatment-related deaths occurred in either group.
Conclusions. Our results demonstrated similarities in terms of toxicity and efficacy to those obtained by weekly and biweekly administration of cetuximab with combined FOLFIRI chemotherapy in Taiwanese patients.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2010;21:59-68*]

Received: July 14, 2009. Accepted: September 7, 2009.
Correspondence to: Prof. Jaw-Yuan Wang, Department of Surgery, Kaohsiung Medical University Hospital, No. 100, Tzyou 1st Road, Kaohsiung 807, Taiwan. Tel: +886-7-312-2805; Fax: +886-7-311-4679; E-mail: cy614112@ms14.hinet.net

In frequency of incidence of all cancers, colorectal cancers (CRC) rank fourth in men and third in women with approximately 1 million new cases in 2002 (9.4% of the world total), and 529,000 deaths due to CRC are reported around the world annually.[1] In Taiwan, colorectal cancer is one of the most common malignancies. The incidence of colorectal cancer in Taiwan is 35.06/100,000 in 2004; gradually approaching Western figures in recent decades. More than 10,000 new cases of CRC were diagnosed and more than 4,000 Taiwanese died from colorectal cancer in 2007.[2]

Because of the limited response obtained for patients with advanced CRC from first-line chemotherapy (Fluoropyrimidines (FU) modulated by leucovorin (LV)), other therapeutic agents with different mechanisms were obtained later such as Fluoropyrimidine-based combination with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). Using cetuximab (Erbitux®, ImClone Systems Inc, New York, NY, and Bristol-Myers Squibb Co, Princeton, NJ), a monoclonal antibiotic to the epidermal growth factor receptor (EGFR), plus FOLFORI, an overall improved response rate was achieved.[4] While this regimen is undoubtedly active, the agent is typically administrated weekly combined with administration of the chemotherapy, which is often administrated every 2 weeks.[3] However, the feasibility, efficacy, safety and economic benefits for biweekly dosing of cetuximab combined with biweekly chemotherapy regimens are supported by several studies in Caucasians.[5] However, all these data were mainly from Western countries, and they may be different for the Taiwanese population.

Herein, the purpose of this article was to compare the two different regimens of weekly and biweekly cetuximab-combination FOLFIRI regimen as first-line setting in patients with metastatic CRC (mCRC) in Taiwan. We focused on the side effects encountered and the efficacy from progression-free survival response in these patients. And this simplified schedule may reduce the costs associated with cetuximab administration.

Materials and Methods

We conducted a retrospective analysis of sixty patients with histologically confirmed mCRC from January 2005 to October 2008. Sixty patients were divided into two groups based on the different regimens of cetuximab. Irinotecan is often administered at a dose of 180 mg/m^2 every 2 weeks with combinations of infusional 5-fluorouracil (5-FU)/folinic acid (LV) (FOLFIRI) in the first-line setting. In group A (weekly), twenty six patients received intravenous (IV) cetuximab weekly (400 mg/m^2 as a 120-min IV infusion at first week, then 250 mg/m^2 as a 60-min IV infusion per-week) combined with chemotherapy of FOLFIRI. In group B (biweekly), thirty four patients received cetuximab biweekly (500 mg/m^2 as a 120-min IV infusion per 2-week) combined with chemotherapy of FOLFIRI. The term "first-line setting" in this study was defined as the first-line cetuximab-combination chemotherapy regimen being used in the patient after identification of their mCRC lesions.

For tumor staging, initial work-up included general history and physical examination, routine blood cell count, biochemistry, and serum carcinoembryonic antigen (CEA) level examination. For further image study, chest X-ray, abdominal echo or abdominal computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed. Bone scan, or positron emission tomography (PET) were performed selectively for those which showed suspicious findings on CT or MRI or specific sites of metastases were suspected.

The clinical records of each patient of this study were retrospectively reviewed. The characteristics of the patients being recorded include age, gender, metastatic sites, the different schedule of cetuximab-combination chemotherapy, and observed toxicities encountered after the chemotherapy. Safety assessment and laboratory tests were performed biweekly. Courses of chemotherapy were continued in the presence of an absolute neutrophil count ≥ 1500/μl and platelet count ≥ 100,000/μl and recovery of any extra-hematological toxicity. Otherwise, for patients with grade 2 or more severe hematologic toxicities, treatment was postponed for one or two weeks until recovery and restarted when it had reduced to grade 2. Both regimens were continued until one of the following occurred: progressive disease, unacceptable adverse effects, the patient refused further treatment with any cetuxi-

mab-combination chemotherapy, or the patient was lost to follow-up.

The primary objectives of this study were to assess the safety and efficacy of these two different dosing regimens of cetuximab-combination chemotherapy. The assessment of toxicities was based on the National Cancer Institute Common Toxicity Criteria (version 2.0). (http://ctep.cancer.gov/reporting/ctc.html; accessed in May 2009). The time for the first response assessment with CT or other imaging study was typically performed 2-3 months after the first assessment. Patient responses were classified according to the Response Evaluation Criteria in Solid Tumors (RECIST).[6]

A complete response (CR) was defined as the disappearance of all target lesions of cancer in response to treatment. A partial response (PR) was defined as at least 30% decrease in the sum of the longest diameter of metastatic lesions, with no evidence of new lesions. A progressive disease (PD) 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 diameter recorded before the patient started to receive treatment. And it could also be defined if identification of one or more new lesions was made. A stable disease (SD) was defined as neither having sufficient shrinkage to qualify for a partial response nor a sufficient increase to qualify for progressive disease.

We report here the best response, which was defined as the best response recorded by the investigators, since the confirmatory image evidence of response obtained every 2-3 months from the first time cetuximab-combination chemotherapy was administered. Also, the progression-free survival was compared between two groups. However, the median overall survival was not analyzed in this study because of the limited period of follow-up in the current study.

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences version 12.0 software (SPSS Inc., Chicago, IL, USA). Descriptive variables of patient characteristics and toxicities were calculated directly from the database. The Chi-squared test of Fisher's exact test was used to compare toxicities and response in the two groups. A probability of less than 0.05 was considered statistically significant. Progression-free survival was defined as the time to documented progression from the start of the treatment and calculated according to Kaplan-Meier methods and compared by log-rank test.

Results

Patient characteristics

The characteristics of these sixty patients are summarized in Table 1. All sixty patients were classified into two groups according to the two different dosing regimens of cetuximab-combination chemotherapy. The median age was 55 years in group A (range, 44 to 86) and 61 years in group B (range, 39 to 78). Within the two different groups, there were 14 males and 12

Table 1. Baseline characteristics of patients

	Group A (%) n = 26	Group B (%) n = 34
Age (years)		
Median	55	61
Range	44-86	39-78
Sex-n (%)		
Male	14 (53.8)	18 (52.9)
Female	12 (46.1)	16 (47)
Primary Site-n (%)		
Colon	21 (80.7)	27 (79.4)
Rectum	5 (19.2)	7 (20.5)
Site of metastases-n (%)		
Liver Only	12 (46.1)	17 (50)
Lung Only	4 (15.3)	5 (14.7)
Local recurrence with peritoneum	3 (11.5)	3 (8.8)
Bone Only	0 (0)	1 (2.9)
Brain Only	0 (0)	1 (2.9)
Ovary Only	1 (3.8)	0 (0)
Distal LN	1 (3.8)	0 (0)
Multi-organ sites	5 (19.2)	7 (20.5)
***KRAS* Mutation status**		
Mutations	11 (42.3)	14 (41.2)
Wild type	15 (57.7)	20 (58.8)
EGFR Overexpressiom		
Positive	20 (76.9)	25 (73.5)
Negative	6 (23.1)	9 (26.5)

Group A: Cetuximab used weekly; Group B : Cetuximab used biweekly
EGFR: Epidermal growth factor factor

females in group A, and 18 males and 16 females in group B. Among 26 patients of group A, there were 21 patients (80.7%) with primary tumors located in the colon and 5 patients (19.2%) with tumors located in the rectum. Among 34 patients of group B, 27 patients (79.4%) had primary tumors located in the colon and 7 patients (20.5%) had them located in the rectum. The main site of metastases was liver (46.1% in group A, 50% in group B), followed by lung (11.5% in group A and 8.8% in group B) and local recurrence (15.3% in group A and 20.5% in group B). 19.2% in group A and 14.7% in group B had metastases in more than one site. In group B, there was one patient who had bone metastases only without radiotherapy because of the short time of survival and intolerance to radiotherapy; another patient who had multiple brain metastases only with poor response under cetuximab- combination chemotherapy. Otherwise, there was one patient with left side ovary metastases in group A, and resection of left side ovary was performed at the same time with anterior resection. However, local recurrence happened one more years after operation and cetuximab-combination chemotherapy. Besides, we analyzed all the patient in both groups about activating *KRAS* mutations and overexpression of epidermal growth factor receptor. Eleven patients (42.3 %) in group A had *KRAS* mutations and fourteen patients (41.2%) in group B. About epidermal growth factor receptor, there are twenty patients (76.9%) in group A and twenty-five patients (73.5%) in group had overexpression of epidermal growth factor receptor.

Efficacy

A total of 26 patients in group A who underwent weekly cetuximab-combination chemotherapy and 34 patients in group B who underwent bi-weekly cetuximab-combination chemotherapy were assessed for responses. The main objective responses of these patients are summarized in Table 2. Among the 26 patients in group A, complete response was observed in one case (3.8%); partial response was observed in 14 cases (53.8%); stable disease was observed in 5 cases (19.2%) and progressive disease was observed in 6 cases (23.1%). For the 34 patients in group B, one patient (2.9%) had complete response, 20 patients (58.8%) had partial response, 7 patients (20.5%) had stable disease and 6 patients (17.6%) had progressive disease. Overall, the disease control rate (complete response + partial response + stable disease) reached 76.8% (20/26) in group A and 82.4% (28/34) in group B ($p = 0.602$). Fig. 1 shows the progression-free survival Kaplan-Meier curve of these two different dosing groups.

Table 2. Efficacy of patients receiving cetuximab-combined FOLFIRI chemotherapy

	Group A (%) n = 26	Group B (%) n = 34	*p*
Disease Control Rate	20 (76.8)	28 (82.4)	
Complete response	1 (3.8)	1 (2.9)	
Partial response	14 (53.8)	20 (58.8)	0.602
Stable disease	5 (19.2)	7 (20.5)	
Progress disease	6 (23.1)	6 (17.6)	

Group A: Cetuximab used weekly; Group B: Cetuximab used biweekly
Disease Control Rate = Complete Response Rate + Partial Response Rate + Stable disease

The progression-free survival was 12 months in group A and 13 months in group B. Progression-free survival had no significant statistically difference between two groups after analysis ($p = 0.662$). As we mentioned above, the efficacy achieved with the biweekly cetuximab-dosing regimen was shown to be

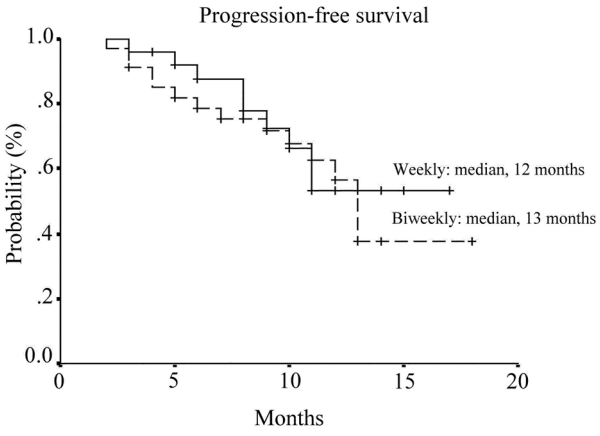

Fig. 1. Analysis of progression-free survival of the metastatic colorectal cancer patients treated with weekly and biweekly cetuximab-combination chemotherapy. The progression-free survival of these two groups was not statistically significant ($p = 0.662$).

similar to the efficacy of the weekly dosing regimen.

Safety

The toxicities and all safety profiles of these two groups are listed in Table 3. All patients in both groups were assessable for toxicity. The most commonly reported side event was hypersensitivity, (a drug-related acne-like skin rash), but in most patients suffering from this rash, it was grade 1 or 2 and easily managed. Three patients (11.5%) suffered from grade 3 or 4 skin rash in group A and five patients (14.7%) in group B without significant difference between the two groups ($p = 1.000$), and most of these hypersensitivity reactions could be treated by antihistamine, with or without steroids.

Neutropenia was the most common grade 3 or 4 adverse event of group A (11.5%, 3/26), consistent with the profile of group B (14.7%, 5/34) ($p = 1.000$) and granulocyte-colony stimulating factors (G-CSF) were administered. Among other hematological side effects including anemia and thrombocytopenia, there were two (7.7%) cases suffering from anemia in group A and two cases (5.9%) in group B ($p = 1.000$); besides, two cases (7.7%) suffered from thrombocytopenia in group A and two cases (5.9%) in group B ($p = 1.000$).

In all cases, all these hematological side effects were usually short-lived and were rarely complicated.

Table 3. Grade 3/4 toxicities of patients receiving cetuximab-combined FOLFIRI chemotherapy

	Group A (%) n = 26	Group B (%) n = 34	*p*
Skin Rash	3 (11.5)	5 (14.7)	1.000
Neutropenia	3 (11.5)	5 (14.7)	1.000
Anemia	2 (7.7)	2 (5.9)	1.000
Thrombocytopenia	2 (7.7)	2 (5.9)	1.000
Diarrhea	3 (11.5)	3 (8.8)	1.000
Stomatitis	1 (3.8)	3 (8.8)	0.626
Elevated AST	1 (3.8)	3 (8.8)	0.626
Elevated ALT	1 (3.8)	4 (11.8)	0.377
Paronychia	3 (11.5)	3 (8.8)	0.121
Alopecia	1 (3.8)	0 (0)	0.443
Fatigue/Asthenia	2 (7.7)	3 (8.8)	0.875

Group A: Cetuximab used weekly; Group B : Cetuximab used biweekly
AST: aspartate transaminase; ALT: alanine transaminas

No patients experienced these side events leading to cessation of therapy. All hematological side effects did not differ significantly between the two groups (all $p > 0.05$). Neither grade 4 myelosuppression nor severe infusional anaphylactic reactions were found in either group.

Rates of toxicity-related gastrointestinal side effects which included nausea, vomiting, anorexia, diarrhea and constipation were similar across these two groups and always could be easily treated. However, grade 3 or 4 diarrhea occurred in 3 patients (11.5%) in group A and 3 patients (8.8%) in group B. 3.8% (1/26) of the patients in group A and 8.8% (3/34) of the patients in group B complained of grade 3 stomatitis. All these gastrointestinal side effects could be easily controlled by antiemetic, antidiarrheal agents and intravenous fluid supplement. In both groups, no therapies were discontinuous consequently. And under the statistical analyses, there were similar safeties in both groups (all $p > 0.05$). Drug-related seriously elevated liver functions were reported in both groups. Elevated AST (aspartate transaminase), was found in one patient (3.8%) and elevated ALT (alanine transaminase) was found in one patient (3.8%) in group A. In group B, the hepatic toxicities were slightly higher with 3 patients (8.8%) having elevated AST and 4 patients (11.8%) having elevated ALT. But in these two different dosing regimens, there were no clinically relevant adverse effects and it seems that there was no significant correlation between different dosing regimen and elevated liver functions (both $p > 0.05$). Concerning other specific side events, paronychia was reported in 11.5% (3/26) of patients in group A and 8.8% (3/34) of patients in group B ($p = 0.121$); alopecia in 3.8% (1/26) of group A and none in group B (0.443); fatigue/asthenia in 7.7% (2/26) of group A and 8.8% (3/34) of group B (0.875). No treatment-related deaths occurred.

Overall, the safety of the biweekly cetuximab dosing regimen was consistent with the weekly dosing regimen without meaningful increase in toxicity. Therefore, the administration of biweekly dosing regimen proved to be well tolerated and the different dosing regimen of biweekly cetuximab did not increase the side effects of chemotherapy.

Discussion

In general, rates of incidence of colorectal cancer are increasing rapidly in countries where overall risk was formerly low (especially in Japan and also elsewhere in Asia),[1] and the same trend in Taiwan. The therapeutic mainstay for CRC is 5-FU/LV regimen. And until recently, the standard systemic treatment of mCRC has been oxaliplatin plus infusional 5-FU/LV (FOLFOX) or infusional 5-FU/LV plus irinotecan regimen (FOLFIRI).[7]

In recent decades, advances in the understanding of the tumor biology from CRC have led to the identification of important cellular processes involved in the pathogenesis, and drugs which interfere with these critical pathways are known as target therapy.[8] EGFR is involved in signaling pathways that affect cellular growth, differentiation, proliferation, and programmed cell death, and is a transmembrane glycoprotein that is often overexpressed in CRC.[9,10] Cetuximab, a chimeric monoclonal immunoglobulin G1 antibody that binds to extracellular domain of the EGFR and inhibits the EGFR, has been found to be effective alone and in combination of irinotecan in patients with mCRC as second- and subsequent-line treatment of mCRC in patients who are refractory to irinotecan-based chemotherapy.[9,11]

The main aim of this retrospective study was to investigate the antitumor activity of the combination of cetuximab and irinotecan-based chemotherapy given in a biweekly fashion. Most chemotherapy regimens from CRC are given every two weeks and therefore it would be more convenient if cetuximab could be administered every two weeks. Although cetuximab is currently administered with a weekly schedule on the basis of previous studies, development of a biweekly dosing regimen for cetuximab would provide treatment flexibility when combined with biweekly chemotherapy regimen, as well as its efficacy and safety profile with respect to the standard weekly regimen used in most trials with cetuximab.[5,13-15] Inspired by pharmacodynamic and pharmacokinetic studies which revealed no significant differences between weekly cetuximab 250 mg/m^2 and biweekly cetuximab 500 mg/m^2, we had simplified the administration of cetuximab biweekly with combination to irinotecan-base chemotherapy.[14] While the pharmacokinetic and pharmacodynamic data suggest the clinical equivalence of the weekly and bi-weekly cetuximab regimen,[14] direct demonstration of the efficacy equivalence of these two different regimens is required.

Our present investigation shows that disease control rate and the progression-free survival of these two different regimen groups was not significantly different between these two groups. In group A, one patient (3.8%) had complete response, 14 patients (53.8%) had partial response and 5 patients had stable response (19.2%) resulting in an overall disease control rate of 76.8% (20/26). In group B, one patient (2.9%) had complete response, 20 patients (58.8%) had partial response and 7 patients had stable response (20.5%) resulting in an overall disease control rate of 82.4% (28/34). This result is compatible with the results of several previous studies from Western countries,[13-15] and the findings are vital for Taiwanese mCRC patients for the administration of cetuximab weekly or biweekly.

The adverse events reported here are typical of those expected with cetuximab with irinotecan. Administration of a high dose of cetuximab with biweekly regimen is not associated with a greater incidence of grade 3 or 4 adverse events than weekly administration of the lower, approved dose in previous studies.[13,16] In our study, the results presented here for the biweekly dosing regimen of 500 mg/m^2 revealed toleration for a weekly dose of 250 mg/m^2. There were three patients (11.5%) suffering from grade 3/4 skin rash in group A and five patients (14.7%) in group B respectively. A low percentage of patients with grade 3 or 4 neutropenia/anemia/thrombocytopenia was found in our investigation and in these patients, granulocyte-colony stimulating factors was given for neutropenia and the side events were controlled, and all treatment could be carried on thereafter. Besides, no treatment was stopped due to anemia or thrombocytopenia. Additionally, most hypersensitivity reactions were easily treated by antihistamine, with or without steroids.

Gastrointestinal side events as nausea or vomiting were always mild to moderate and were controlled with standard antiemetics. Even grade 3 or 4 diarrhea occurring in both groups (11.5% versus 8.8%) as well

as stomatitis (3.8% versus 8.8%), were all easily treated by supportive management. The rate and severity of patients developing mild to moderated gastrointestinal toxicities were lower than previous reports.[18,19] The cause of low grade 3 or 4 diarrhea might result from the lesser frequencies of 6/7 and 7/7 genotypes of *UGT1A1* in Taiwanese subjects.[20] A low percentage of patients with elevated AST/ALT, fatigue, paronychia, alopecia were found in our investigation and no severe toxicities occurred. In both groups, no patients lost further treatment because of the adverse events encountered, and in terms of toxicity, the biweekly dosing regimen had proved to be well tolerated. Simplified cetuximab does not increase the rate and risk of the adverse events or toxicities.

In the initial 60 treated Taiwanese patients of our study, we found no significant difference in efficacy and toxicity in both groups. The option to synchronize the administration of cetuximab and concomitant chemotherapy would reduce the impact of treatment administration on patients' lives and simplify treatment administration for health care worker. It is also reasonable to assume that this simplified schedule would probably reduce the costs associated with cetuximab administration. Consequently, we suggested that biweekly dosing cetuximab-combination chemotherapy is an effective regimen with acceptable toxicities, and should be considered as an optional first-line setting for Taiwanese patient populations with mCRC. Besides, Activating *KRAS* mutants is an important independent predictive marker in mCRC treated with cetuximab plus chemotherapy and EGFR could help to identify the subgroup of patients who are most likely to respond to cetuximab plus chemotherapy.[21] Further prospective studies on larger mCRC cases are need to definitely establish the clinical relevance of *KRAS* mutation and EGFR.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics. 2002. *Cancer J Clin* 2005;55:74-108.
2. Statistics on Leading Causes of Cancer Death, Department of Health, Executive Yuan, Taiwan, ROC, 2007.
3. Mitry E, Lièvre A, Bachet JB, Rougier P. Irinotecan as palliative chemotherapy for metastatic colorectal cancer: evolving tactics following initial treatment. *Int J Colorectal Dis* 2009; 24:605-12.
4. Min BS, Kim NK, Ahn JB, Roh JK, Kim KS, Choi JS, Cha SH, Kim H. Cetuximab in combination with 5-fluorouracil, leucovorin and irinotecan as a neoadjuvant chemotherapy in patients with initially unresectable colorectal liver metastases. *Onkologie* 2007;30:637-43.
5. Ramanathan RK. Alternative dosing schedules for cetuximab: a role for biweekly administration? *Clin Colorectal Cancer* 2008;7:364-8.
6. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van GM, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European organization for research and treatment of cancer, national cancer institute of the United States, national cancer institute of Canada. *J Natl Cancer Inst* 2000;92:205-16.
7. Fakih M. The role of targeted therapy in the treatment of advanced colorectal cancer. *Curr Treat Options Oncol* 2008;9: 357-74.
8. Reidy D, Saltz L. Targeted strategies in the treatment of metastatic colon cancer. *J Natl Compr Canc Netw* 2007;5:983-90.
9. Midgley RS, Yanagisawa Y, Kerr DJ. Evolution of nonsurgical therapy for colorectal cancer. *Nat Clin Pract Gastroenterol Hepatol* 2009;6:108-20.
10. Hemming AW, Davis NL, Kluftinger A, Robinson B, Quenville NF, Liseman B, LeRiche J. Prognostic markers of colorectal cancer: an evaluation of DNA content, epidermal growth factor receptor, and Ki-67. *J Surg Oncol* 1992;51: 147-52.
11. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, Bets D, Mueser M, Harstrick A, Verslype C, Chau I, Van Cutsem E. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*. 2004;351:337-45.
12. Pfeiffer P, Nielsen D, Yilmaz M, Iversen A, Vejlø C, Jensen BV. Cetuximab and irinotecan as third line therapy in patients with advanced colorectal cancer after failure of irinotecan, oxaliplatin and 5-fluorouracil. *Acta Oncol* 2007;46:697-701.
13. Martín-Martorell P, Roselló S, Rodríguez-Braun E, Chirivella I, Bosch A, Cervantes A. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br J Cancer* 2008;99:455-8.
14. Tabernero J, Pfeiffer P, Cervantes A. Administration of cetuximab every 2 weeks in the treatment of metastatic colorectal cancer: an effective, more convenient alternative to weekly administration? *Oncologist* 2008;13:113-9.
15. Pfeiffer P, Nielsen D, Bjerregaard J, Qvortrup C, Yilmaz M, Jensen B. Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. *Ann Oncol* 2008;19:1141-5.
16. Tabernero J, Cervantes A, Martinelli E, Vega-Villegas E, Rojo F, Pérez-Fidalgo A, Casado E, Ciardiello F, Eubel A,

Baselga J. Optimal dose of cetuximab given every 2 weeks (q2w): A phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly (q1w) and q2w schedules in patients (pts) with metastatic colorectal cancer (mCRC). *J Clin Oncol* 2006;24(18 suppl):142s.

17. Ma CJ, Hsieh JS, Chen FM, Chen HM, Huang CJ, Huang TJ, Wang JY. Oxaliplatin/5-Fluorouracil/Leucovorin (FOLFOX4) in metastatic colorectal cancer (CRC). *J Soc Colon Rectal Surgeon (Taiwan)* 2007;18:65-72.
18. Kallen KJ, Hofmann MA, Timm A, Godderz W, Galle PR, Heike M. Weekly oxaliplatin, high-dose infusional 5-fluorouracil and folinic acid as palliative third-line therapy of advanced colorectal carcinoma. *Z Gastroenterol* 2000;38:153- 7.
19. Giacchetti S, Perpoint B, Zidani R, Le Bail N, Faggiuolo R, Focan C, Chollet P, Llory JF, Letourneau Y. Phase III multicenter randomized trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2000;18:136-47.
20. Tsai HL, Chen CF, Lu CY, Fang WF, Wu DC, Wu IC, Sheen MC, Lin SR, Wang JY. Significant correlation between polymorphisms of *UGT1A1* gene and low irinotecan toxicity in colorectal cancer patients with FOLFIRI. *Open Colorectal Cancer J*. (Accepted in 2009).
21. Yen LC, Uen YH, Wu DC, Lu CY, Yu FJ, Wu IC, Lin SR, Wang JY. Activating *KRAS* mutations and overexpression of epidermal growth factor receptor as independent predictors in metastatic colorectal cancer patients treated with cetuximab. *Ann Surg*. (Accepted in 2009).

原　著

轉移性結直腸癌病患以兩種不同的給藥頻率 (每週以及雙週) 投與 cetuximab 合併 FOLFIRI 化學治療處方做為第一線治療的有效性及安全性比較---單一南台灣醫學中心之經驗

葉永松 [1,2]　蔣政穎 [1]　陳欽凡 [1]　馬政仁 [1]　陳芳銘 [1,3]　陳漢文 [1,3]
黃哲人 [1,3]　謝建勳 [1,3]　王照元 [1,3]

高雄醫學大學附設中和紀念醫院　胃腸及一般外科 [1]　外傷科 [2]
[3] 高雄醫學大學醫學院　醫學系

目的　此回溯性研究的目的主要是在比較兩種不同的給藥頻率 (每週以及雙週) 投與 cetuximab 合併 FOLFIRI 化學治療處方，用於第一線治療南台灣轉移性之結直腸癌病患的有效性及毒性。

方法　從 2005 年 1 月到 2008 年 12 月，我們針對共 60 位在本院接受 cetuximab 合併 FOLFIRI 化學治療之轉移性結直腸癌病患之病歷資料進行回溯性分析。依據所使用處方的不同頻率，我們將病患分成兩組加以分析：在 A 組中 (每週處方)，總共有 26 位病患在第一個星期接受 400 mg/m^2 劑量之 cetuximab，點滴注射 120 分鐘，合併點滴注射之標準 FOLFIRI 化學治療，之後以每週的頻率施打 250 mg/m^2 之 cetuximab，點滴注射 120 分鐘，合併點滴注射之標準 FOLFIRI 化學治療。在 B 組中 (雙週處方)，總共有 34 位病患以每兩個星期的頻率接受 500 mg/m^2 劑量之 cetuximab，點滴注射 120 分鐘，合併點滴注射之標準 FOLFIRI 化學治療。根據實體腫瘤反應評估標準 (response evaluation criteria in solid tumors) 我們記錄了每位病患的病史、特徵、接受化學治療後的反應及治療過程中所遭遇的毒性。

結果　A 組及 B 組的病患接受 cetuximab 合併化療後的總疾病控制率分別爲 76.8% 和 82.4% (p = 0.602)。A 組及 B 組病患在開始接受化療後的無疾病進展存活期 (progression-free survival) 分別爲 12 個月和 13 個月 (p = 0.662)。在統計學上的分析比較上兩組之間並無顯著的差異。在毒性分析方面，A 組及 B 組的病患發生第三或第四級腹瀉的比率爲 11.5% 和 8.8%；發生第三級皮膚過敏反應得比率分別爲 11.5% 和 14.7%；發生第三級或更嚴重的嗜中性球缺乏症/貧血/血小板低下的比率分別爲 11.5%/7.7%/7.7%

(A 組) 和 14.7%/5.9%/5.9% (B 組)。這些毒性在統計學上的分析比較，在兩組之間均無顯著的差異，並且在接受適當治療後均可以獲得顯著的改善。治療過程中，沒有病人因爲藥物毒性而死亡。

結論 我們的研究發現，對台灣發生轉移性結直腸癌病患之治療，雙週給予 cetuximab 合併 FOLFIRI 化療就如同單週給予 cetuximab 合併 FOLFIRI 化療一樣，都是相對安全且病患耐受性佳的處方，兩者也均可被接受作爲治療這類病患的第一線化療處方。

關鍵詞 雙週、cetuximab、轉移性結直腸癌、安全性、有效性。