Decreasing Dosage of Irinotecan, 5-Flurouracil (5-FU) and Leucovorin (LV) in the Treatment of Advanced and /or Metastatic Colorectal Cancer: A Phase II Study

Jen-Seng Huang, MD; Cho-Li Yen[1], MD; Yao-Tong You[2], MD; Chen-Hsu Wang, MD; Yii-Jenq Lan, MD; Chien-Hong Lai, MD; Tsung-Cheng Chueh, MD; Chung-Chi Liaw[3], MD

Background: In this study, we attempted to determine the efficacy and toxicity of decreasing dosage of irinotecan plus 5-fluorouracil (5-FU) and leucovorin (LV) in the treatment of advanced colorectal cancer.

Methods: A total of 250 mg/m^2 Irinotecan (CPT-11) intravenous infusion for 90 minutes was administered every 3 weeks. A 24-hour intravenous infusion with 2000 mg/m^2 5-FU and 200 mg/m^2 LV was administered through a port-A catheter system weekly for 2 consecutive weeks. Each treatment cycle was repeated every 3 weeks. Progression-free survival and survival curves were drawn according to Kaplan-Meier method. Tumor responses were determined according to the RECIST guidelines. Toxicities were evaluated using the WHO criteria.

Results: Thirty-eight patients were enrolled from September 2001 through October 2004. The median number of treatment courses was 8.1 (range, 1-14). Based on the intent-to-treat principle, the response rate was 39.5% (95% CI: 25.4-54.4%) which included 5.3% complete response (CR) and 34.2% partial response (PR). The time to tumor progression was 8.4 months (range, 2-12 months). The median time of survival was 18.4 months (range, 4-26 months). The major toxicities were grade 1 neutropenia and grade 2 diarrhea. Toxic death was not found in this study. The efficacy of this regimen was compatible with the reports of the clinical trials in the United States and European countries but fewer incidence of toxicity was found in our results.

Conclusion: The results revealed that our combination regimen of 5-FU/LV + CPT-11 is a highly effective and acceptable protocol. This treatment is easily performed in an outpatient clinic. The biggest advantage is that all patients were intensively cared by the physicians to maintain a quality of life, and only 26.3% of patients showed progressive disease. Therefore, this regimen may be considered to be used in the treatment of patients with terminal cancer. A further randomized study comparing this regimen with oral fluoropyrimidines plus irinotecan is warranted.

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Key words: advanced colorectal cancer, metastatic, irinotecan, 5-fluorouracil, leucovorin.

From the Department of Hemato-Oncology, [1]Department of Gastroenterology, [2]Department of Proctology, Chang Gung Memorial Hospital, Keelung, College of Medicine, Chang Gung University; [3]Department of Oncology, Chang Gung Memorial Hospital, Taipei, College of Medicine, Chang Gung University.

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Correspondence to: Dr. Jen-Seng Huang, Division of Hemato-Oncology, Chang-Gung Memorial Hospital. 222, Maijin Rd., Anle Chiu, Keelung, Taiwan 204, R.O.C. Tel.: 866-2-24313131 ext. 3168; Fax: 886-2-24335342; E-mail: ruby800@cgmh.org.tw

Colorectal cancer has become a common cancer in Taiwan.[1] Resection of the primary tumor is the standard treatment for patients with localized disease and may offer an opportunity for cure. For patients with resectable disease, adjuvant therapy with cytotoxic drugs, with or without radiotherapy were usually performed after curative surgery. However, 30%-40% of these patients still relapsed after adjuvant therapy. Furthermore, approximately 20%-30% of the patients have metastatic disease at presentation; thus, more than 50% of the patients cannot be controlled using curative surgery.[2] To induce tumor remission, control disease progression, and prolong life when maintaining the quality of life were our objectives of palliative chemotherapy for advanced colorectal cancer.

The chemotherapeutic agent 5-fluorouracil (5-FU) has remained the most widely used in the patients with colorectal cancer since its synthesis in 1957. 5-FU has traditionally been administered as an intravenous bolus or continuous infusion. Objective response rates are typically around 20% and the median survival was approximately 1 year when 5-FU was utilized as first-line monotherapy. However, the most efficacious dosage, treatment interval, and mode of administration (infusion or bolus) of 5-FU is still being debated.[3,4] Recently, several new agents such as irinotecan and oxaliplatin have been developed to treat the metastatic colorectal cancer.[5-9] The single-agent oxaliplatin demonstrated a response rate of approximately 10% in patients whose disease progressed after a 5-FU based regimen.[10] Adding oxaliplatin to 5-FU regimens in previously treated patients stimulated response in 25%-30% of the patients.[11] For previously untreated patients, the response rate was around 40%-60% with a median survival in excess of 15 months.[12,13] Nevertheless, the unacceptable peripheral neurotoxicity made the accumulative dosage of oxaliplatin limited.[10-13]

As a semi-synthetic derivative of camptothecin, irinotecan targets topoisomerase I, the enzyme that catalyses the cleavage and resealing of supercoiled DNA, and is essential for DNA replication and transcription.[2] Monotherapy using irinotecan for colorectal cancer on an every 3 week regimen supported the premise of non-cross-resistance between 5-FU and irinotecan.[14] To date, results of trials of 5-FU (in combination with or without leucovorin) plus irinotecan have been encouraging, and showed advantages in response rates and times to disease progression over 5-FU alone.[15] More recently, further clinical trials have been administered to investigate the efficacy and safety of irinotecan in combination with 5-fluorouracil (5-FU) and leucovorin (LV) as a first-line therapy. From the reports of the trials, the response rates were around 40%-50% whereas the incidence of toxicities including myelosuppression and diarrhea were 40% and 35%, respectively.[5-7] In recent randomized trials in patients with 5-FU resistant disease, irinotecan was shown to significantly prolong survival compared with either the best supportive care or continuous infusion of 5-FU alone.[16,17] Although several studies with irinotecan and 5-FU regimen demonstrated added benefits to advanced or metastatic colorectal cancer patients, however, most prior studies concentrated on weekly, biweekly or schedules every 3 week of irinotecan.[14-17] In addition, high toxicity rates of irinotecan including myelosuppression and delayed diarrhea have been a concern. There have been few reports evaluating two consecutive weekly schedules of 5-FU/LV infusion in combination with altered dosage of irinotecan. Different dosages of irinotecan and 5-FU/LV should have different results of efficacy and toxicity. Therefore, this trial was designed to evaluate the efficacy and toxicity of decreasing dosage of every 3 week irinotecan and 2 consecutive weekly 5-FU/LV in the treatment of advanced and /or metastatic colorectal cancer.

METHODS

This single-center, prospective, open-label, phase II study evaluated the efficacy and toxicity of decreasing dosage of irinotecan and 5-FU/LV in the treatment of advanced and/or metastatic colorectal cancer. Secondary objectives were to evaluate the time to disease progression and overall survival. All patients were required to provide written informed consent before participating in this study.

From September 2001 through October 2004, 38 adult patients with metastatic colorectal carcinoma were eligible for this study. All patients were histologically proven to have advanced inoperable or metastatic adenocarcinoma of the colon or rectum. All patients had never received prior systemic chemotherapy for metastatic diseases. Nevertheless, prior adjuvant chemotherapy was allowed if it had

been completed at least 6 months before the commencement of this study. For the patients to be eligible, the following were required: a bi-dimensionally measurable disease on chest x-ray or computer tomography (CT scan) outside any previous irradiated zone, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, age ≤ 70 years old, no severe medical diseases or central nervous system metastasis, and no previous history of any other malignancy except curatively treated non-melanoma skin cancer or cervical carcinoma in situ.[18] All patients were also required to have normal hematopoietic function as evidenced by absolute neutrophil counts (ANC) ≥ 1.5×10^9/l and platelet counts ≥ 100×10^9/l. Patients with any active infections were not enrolled. Pregnant or breast-feeding patients were also excluded. Each patient had to have serum transaminase less than three times the upper normal limit. All patients were required to have recovered from the effects of recent surgeries or radiotherapy at least 4 weeks apart. A signed, written informed consent was obtained from each patient after the full explanation.

A total of 250 mg/m^2 Irinotecan in 300 ml isotonic sodium chloride solution IV infusion for 90 minutes was administered every 3 weeks. A total of 2000 mg/m^2 5-FU and 200 mg/m^2 leucovorin were given using 24-hour IV infusion through a Port-A catheter system weekly for 2 consecutive weeks. Each treatment cycle was repeated every 3 weeks. IV injection of 0.5 mg Atropine was given before irinotecan infusion and oral loperamide p.r.n. if delayed diarrhea occurred.

For the patients with ANC < 1.5×10^9/l or platelet counts < 100×10^9/l after chemotherapy, the regimen was postponed for 1 week. If the platelet counts were between 60×10^9/l and 100×10^9/l or ANC were between 1.0×10^9/l and 1.5×10^9/l, the dosage of irinotecan was reduced by 25%. If grade 3 or 4 delayed diarrhea toxicity appeared in patients, they had to recover completely within a maximum of 2 weeks and the dosage of irinotecan was reduced by 25% in subsequent cycles. If grade 3 or 4 mucositis or hand-foot syndrome developed, the dosage of 5-FU was reduced by 25%. Additionally, if the regimen could not be conducted within the 2 weeks following the beginning of therapy, the patient was be excluded from this study.

Before initiating therapy, all patients underwent evaluation including a complete medical history, physical examination, complete blood count, blood chemistry, renal, liver function test, ECG, chest PA, abdominal CT scan and routine laboratory studies to define the extent of the disease. Adverse reactions were evaluated utilizing the World Health Organization (WHO) criteria during each treatment course.[19] Tumor-related symptoms were recorded using a 15-point checklist at baseline and at each hospital visit. CEA was measured at least once every 8 weeks. A reduction in CEA concentration was considered a biological effect in patients whose CEA levels had been raised at baseline, but was not used to evaluate response. At the end of study treatment, all patients were followed up monthly to analyze the overall survival and the time to tumor progression.

The patients were monitored for anti-tumor response using repeated CT measurements of indicator lesions every 2 months, and every 3 months after discontinuation of the chemotherapeutic treatment during the first year and every 6 months during the second year. All patients had to receive at least two cycles to be evaluated for a response. The trial was stopped if any of the following conditions occurred such as progressive disease, intolerable adverse events or poor performance status. After the patients were excluded from the trial, they received either supportive treatment or other palliative chemotherapeutic regimens. If a response was documented, then a CT scan was repeatedly checked at least 4 weeks after the previous CT scan and subsequently every 2 months. The effects of treatment were categorized as a complete or partial response. Tumor responses were determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[20] Complete response (CR) was defined as a complete disappearance of all known lesions documented by two different observations at least 4 weeks apart and without the appearance of any new lesion. Partial response (PR) was defined as at least a 30% reduction in the sum of the longest perpendicular diameters of all measurable disease with no new lesion appearing and none progressing for at least 4 consecutive weeks. Stable disease (SD) was defined as < 30% reduction or < 20% increase in the sum of the longest perpendicular diameters of all measurable lesions, with no new lesions appearing for at least 4 weeks. Progressive disease was defined as at least a 20% increase in the sum of the longest diameters or a

detection of new lesion.

From the beginning of chemotherapy, progression-free survival and survival curves were drawn according to the Kaplan-Meier method. Tumor responses were determined according to the RECIST guidelines. Toxicities were evaluated utilizing the WHO criteria. Time to tumor progression (TTP) was calculated from the date of initiation of therapy to the date when progressive disease was first detected. Time of survival was calculated from the date of inclusion until death.

RESULTS

This study prospectively analyzed a total of 38 patients. The median age was 62 years (range, 23-70 years). Twenty-six patients were men, and 12 patients were women. Before the beginning of chemotherapy, 22 patients presented with the performance status 0-1 (ECOG). The remaining 16 patients were in the performance status 2 (ECOG). Of the 38 patients, 24 had liver metastases, 12 had lymph node(s) metastases, 4 had metastatic lung lesions, three of the patients had both liver and lung metastases and one patient had soft tissue metastasis. The colon was the primary tumor site in 22 patients and rectum in 16 patients. Table 1 shows the list of the characteristics of the 38 patients.

All 38 patients had received a total of 288 courses of treatment. The median number of treatment courses was 8.1 (range, 1-14). Totally, there were 5 courses of delayed treatment due to adverse events. More than 98% of treatment courses showed no interruption or delayed treatment. The dosage of irinotecan was decreased by 25% in 2 patients and another patient needed dosage reduction of 5-FU. Only 2 patients withdrew from the study owing to personal reasons that were unrelated to toxicity. According to the intent-to-treat principle, the response rate was 39.5% (95% CI: 25.4-54.4%) which included 2 CR (5.3%) and 13 PR (34.2%). The median time to tumor progression was 8.4 months (range, 2-12 months). The progression-free survival (PFS) curve is illustrated in Figure 1. The median time of survival was 18.4 months (range, 4-26 months). The overall survival curve is shown in Figure 2. Table 2 shows a summary of the response data including the response to the target organ. Sonogram, CT scan, or chest x-ray confirmed the responses of all involved lesions.

All patients were assessable for toxicity. The toxicity levels were generally tolerable. The main toxicities were grade 1 neutropenia and grade 2 diarrhea. Gastrointestinal toxicities including nausea, vomiting and diarrhea were the major adverse events, but these complaints were usually mild and were easily managed by symptomatic treatment. Grade 3 neutropenia was noted in 2 patients. Grade 3 anemia was observed in one patient. Thrombocy-

Table 1. Patients' Characteristics

Characteristics	Number
No. of patients	38
Age (years)	
Median	62
Range	23-70
Gender	
Male	26
Female	12
Performance status (ECOG)	
ECOG 0	2
ECOG 1	20
ECOG 2	16
Primary tumor	
Colon	22
Rectum	16
Course of treatment	
Total	288
Median	8.1
Range	1-14
Site of metastases	
Liver	24
Lymph node(s)	12
Lung	4
Liver and lung	3
Soft tissue	1

Abbreviation: ECOG: east cooperative oncology group.

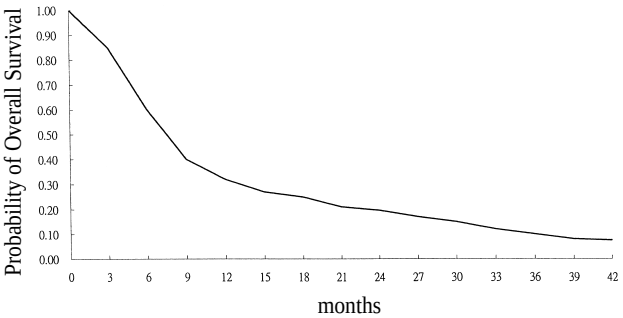

Fig. 1 Progression-free survival (PFS) curve

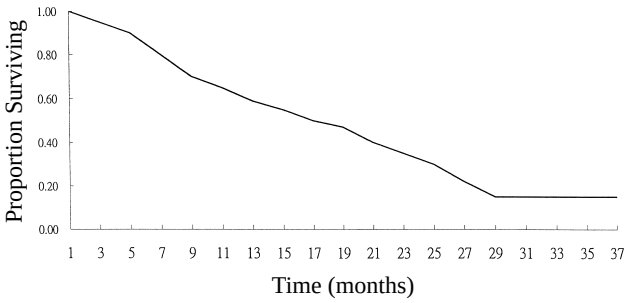

Fig. 2 Overall survival curve

Table 2. Response to Chemotherapy

	Overall	Liver	Lung	LN	Multiple
CR	5.3% (2/38)	1/24	1/4	1/12	0/3
PR	34.2% (13/38)	5/24	1/4	6/12	1/3
SD	34.2% (13/38)	-----	-----	-----	-----
PD	26.3% (10/38)	-----	-----	-----	-----

Abbreviations: CR: complete response; PR: partial response; SD, stable disease; PD: progressive disease; Liver: tumor located in liver; Lung: tumor located in lung; LN: tumor located in lymph node(s); Multiple: tumor located in both liver and lung.

topenia did not exceed grade 1. Grade 3 diarrhea and grade 3 fatigue were reported in one patient, respectively. Neurotoxicities were reported in 6 patients, and grade 1-2 was found in a majority of them. One patient developed a transient painful fissuring erythroderma over his palms and soles (grade 3 hand-foot syndrome). Therefore, this patient received a decreased dosage of 5-FU by 25%. Grade 4 toxicity was not found and there was no treatment-related death in this study. Toxicities were evaluated and are summarized in Table 3.

DISCUSSION

Although continuous-infusion of 5-FU offers theoretical advantages over bolus administration, however, increasing results of trials suggested that the combination regimens were more beneficial than the traditional monotherapy.[5,8,15] Optimizing first-line treatment of metastatic colorectal cancer still remains an immense challenge in treating this disease. The treatment options for patients with advanced colorectal cancer are expanding rapidly.[7,10,12,21,22] According to a report at the 1999 Annual Meeting of the American Society of Clinical Oncology, a survival

Table 3. Treatment-Related Toxicity, Graded According to WHO Criteria (n = 38)

Toxicity	Grade				Total (%)
	1	2	3	4	
Neutropenia	4 (10.5%)	2 (5.3%)	2 (5.3%)	0	8 (21.1%)
Diarrhea	3 (7.9%)	4 (10.5%)	1 (2.6%)	0	8 (21.1%)
Anemia	4 (10.5%)	2 (5.3%)	1 (2.6 %)	0	7 (18.4%)
Fatigue	5 (13.2%)	1 (2.6%)	1 (2.6%)	0	7 (18.4%)
Nausea	5 (13.2%)	2 (5.3%)	0	0	7 (18.4%)
Mucositis	4 (10.5%)	3 (7.9%)	0	0	7 (18.4%)
Neurotoxicity	4 (10.5%)	2 (5.3%)	0	0	6 (15.8%)
Vomiting	3 (7.9%)	3 (7.9%)	0	0	6 (15.8%)
Hand-foot syndrome	3 (7.9%)	1 (2.6%)	1 (2.6%)	0	5 (13.2%)
Thrombocytopenia	3 (7.9%)	0	0	0	3 (7.9%)
Hepatic	0	0	0	0	0
Renal	0	0	0	0	0
Cardiac	0	0	0	0	0

Abbreviation: WHO: world health organization.

advantage with the combination regimen also exists (16.8 months for irinotecan/5-FU/LV vs. 14 months for 5-FU/LV, $p = 0.03$).[14] In addition, the combination of CPT-11 with weekly or biweekly infusional 5-FU/LV (Arbeitsgemein-shaft Intrinisch Oncologie and de Gramont schedules, respectively) were considered the gold standard regimen for the treatment of metastatic colorectal cancer in Europe.[5,9,14,16,22,23] Douillard et al also reported that irinotecan achieved a response rate of 34.8% with a median duration of response of 9.3 months.[5] The median time to disease progression and survival were 6.7 months and 17.4 months, respectively. Impressively, the toxicity was acceptable (0.4% treatment-related death rate). Nevertheless, in a series in the United States, the combination of CPT-11 and weekly bolus 5-FU plus LV (Saltz regimen) showed that the response rate was 39%. The median time to disease progression and overall survival were 7.0 months and 14.8 months, respectively. Unfortunately, a relatively high toxicity level was found (0.9% treatment-related death rate).[24] A combined analysis was carried out which confirmed the results of the above two randomized trials because the inclusion criteria were similar in both studies.[25] Additionally, Sargent et al reported their preliminary estimates of 60-day death rates from any cause in two ongoing studies with CPT-11, LV and 5-FU in the treatment of colorectal

cancer. In both studies, higher death rates were observed in the treatment arm using the Saltz regimen.[26] Conversely, our regimen utilizing decreasing dosages of irinotecan and 5-FU intravenous infusion during this phase II study showed high response rates and also no treatment-related deaths.

In a large randomized study, de Gramont et al compared weekly or biweekly 5-FU/LV with the same regimen plus irinotecan in 385 patients. The addition of iritenocan to the 5-FU/LV regimen significantly improve the response rates (41 versus 31%; $p < 0.001$ for evaluated patients; 35 versus 22%; $p < 0.005$ for intent-to-treat population) and prolonged the median time to tumor progression (median 6.7 versus 4.4 months; $p < 0.001$). Survival was also superior in the irinotecan group (median 17.4 versus 14.1 months; $p = 0.031$).[23] Based on the intent-to-treat principle, our present phase II trial still presented with a response rate of 39.5% which was compatible with the reports of both Saltz regimen and de Gramont schedules. With a maximum follow-up of 37 months at the time of this report, the median time to disease progression and survival were 8.4 months and 18.6 months, respectively. The results of survival and time to disease progression in our study were also compatible with the reported results of some clinical trials in the United States and European countries.[27-31] Generally, the majority of patients endured this modified regimen well. The most frequently observed side effects in this study were neutropenia and diarrhea. Seven patients (18.4%) developped grade 1-2 diarrhea, nevertheless, grade 3 diarrhea occurred in only 1 patient (2.6%). This amount was less than what was reported in previous irinotecan studies (13% and 28%, respectively).[7,31] The results might have been due to the decreasing dosage of irinotecan in this trial. In other reports, the incidence of grade 3 neutropenia were 7% and 7.5%, respectively.[7,22] In this study, only two patients (5.3%) developed grade 3 neutropenia. Therefore, the infection rate was decreased and the nutrition status was improved for these patients. Additionally, grade 3 events for anemia and fatigue were only found in one patient, respectively. In this trial, only 2 patients decided to withdraw from the protocol and did so after receiving one treatment cycle. The intent-to-treat principle is still followed. These 2 patients were classified with progressive diseases. Although the present study had the limitations of a phase II study (limited number of patients and the selection bias), the patient population was representative of this particular disease.

The toxic extent of mucositis and hand-foot syndrome did not increase although the dose of LV differed from that in previous studies. This finding may be due to a decreasing dosage of the weekly 5-FU infusion. In this study, all patients received 2 consecutive weekly infusions of 5-FU and LV, followed by 2 weeks of rest. This protocol offered not only more intensive observation of the patients by the outpatient services, but also appropriate mental support was given by the physicians. Most importantly, patients undergoing this treatment did not need hospitalization and their quality of life was maintained.

Although the dosage of irinotecan was relatively lower when compared with previous studies, the results of the efficacy were encouraging. When irinotecan was given with decreasing dosages, its toxicities were also decreased compared with previous trials. For example, the majority of toxicities were neutropenia, delayed diarrhea, fatigue, anemia, nausea and mucositis in this trial; however, only grade 1 to 2 toxicities occurred in majority of patients. Grade 4 diarrhea (n = 0) or neutropenia (n = 0) were not found which indicated that despite the changing schedules of 5-FU and irinotecan in this study, impressive efficacy and tolerable toxicity were still noted.

The results of this study revealed that decreasing dosages of irinotecan every 3 week and 2 consecutive weekly doses of 5-FU plus LV was a highly effective and well-tolerated regimen. Many first-line treatment for metastatic colorectal cancer studies have been reported, nevertheless, according to the acceptable results of this study, we suggest that physicians should select the best regimen as the first-line treatment rather than waiting for the second-line treatment. The regimen discussed in this study provided good survival results with less toxicity than other regimens for the treatment of patients with terminal colorectal cancer. Therefore, the objectives of prolonging life and maintaining quality of life were obtained. Consequently, further randomized trials should be performed in order to evaluate whether the oral fluoropyrimidines can be combined with irinotecan as first-line therapy with acceptable results at least equivalent to those achieved with irinotecan plus 5-FU/LV in this study.

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用減低劑量後的 Irinotecan, 5-flurouracil (5-FU) and Leucovorin (LV) 治療前進或轉移性大腸直腸癌：Phase II 的研究

黃仁聖 嚴卓立[1] 游耀東[2] 王正旭 藍以政 賴建宏 闕宗正 廖宗琦[3]

背 景： 這個研究企圖用較低劑量的CPT-11 合併 5-FU 及 LV 治療前進性大腸癌並分析其效果及毒性。

方 法： CPT-11 的劑量是 250 mg/m^2，每三星期靜脈注射 90 分鐘，而 5-FU 2000 mg/m^2 及 LV 200 mg/m^2，則是連續兩星期的每星期給予一次靜脈注射 24 小時，這個治療計劃是每三星期爲一個療程，這些藥物都是經由 Port A 人工血管給予。我們是用 Kaplan-Meier 方法，劃出存活期及腫瘤控制期的圖形，而用 RECIST 規範來決定腫瘤反應率。最後是用WHO 的毒性分級準則來評估藥物的副作用。

結 果： 從 2001 年 9 月至 2004 年 10 月間總共收集了 38 個病人進入此臨床試驗。他們接受的平均療程爲 8.1 次 (範圍 1-14 次)，我們是根據積極治療的原則來分析結果，此研究的腫瘤反應率爲 39.5% (95%CI: 25.4-54.4%)，其中包括 5.3% 完全緩解率及 34.2% 的部分緩解率。從接受治療至腫瘤開始惡化的平均時間爲 8.4 月 (範圍 2-12 月)，而平均存活期爲 18.6 月 (範圍 4-26 月)。最主要的毒性爲第一級的白血球顆粒球降低及第二級的的腹瀉症狀，本研究中沒有病人因接受治療而死亡。這個研究用減低化療劑量治療大腸癌的結果並不比歐美各國的臨床試驗差，而毒性卻更低。

結 論： 本研究證明減低劑量後的 CPT-11 合併 5-FU/LV 之化療組合仍是個很有效且病人接受度高的療法。這種療程在門診就可給予。最重要的是這些病人都覺得他們獲得了細心的照顧而且維持了生活品質。本研究只有 26.3% 的病人是一開始就沒效，所以這種療法可考慮用於末期癌症病患的治療。將來應該再作隨機研究來評估口服 fluoropyridium 加上 irinotecan 跟本次研究的方法作個比較。

(長庚醫誌 2006;29:297-305)

關鍵字： 前進性轉移性大腸直腸癌，Irinotecan, 5-flurouracil, Leucovorin。

長庚紀念醫院 基隆院區 血液腫瘤科，[1]胃腸肝膽科，[2]直肛科；[3]長庚紀念醫院 台北院區 血液腫瘤科
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通訊作者：黃仁聖醫師，長庚紀念醫院 血液腫瘤科。基隆市204安樂區麥金路222號。Tel.: (02)24313131轉3168; Fax: (02)24335342; E-mail: ruby800@cgmh.org.tw