5-Fluorouracil and Mitomycin-C: Effective, Low-Cost Chemotherapy for Colorectal Cancer

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Objective: *To evaluate the regimen of 5-fluorouracil (5-FU) and mitomycin-C (MMC) in terms of response rate and overall survival in advanced colorectal cancer.*
Material and Method: *Between January 1993 and December 2000, 121 from 559 patients with advanced colorectal cancer were treated with chemotherapy. Bolus MMC (10 mg/m^2) on first day, 5-FU (600 mg/m^2/day) was given as a continuous infusion for 5 days, repeated every 4 weeks for 6 cycles. Toxicity and response were analyzed according to WHO criteria, and survival was analyzed according to Kaplan-Meier methodology.*
Results: *In the chemotherapy group (121 patients), 70 were males and 51 were females, the mean age was 52 years. The ratio of colon and rectal cancer was 0.57. Nearly all patients (88.89%) had tumors with moderate differentiation. Forty patients with liver metastasis showed an overall response rate of 45% (95% CI 35.4-54.6) with a CR in 3 (7.5%) and PR in 15 (37.5%). The median survival was 13.1 months. The regimen was well tolerated with 11.64% of patients experiencing WHO grade 3-4 toxicity.*
Conclusion: *The present study has indicated a highly active, acceptable toxic, inexpensive regimen of old drugs to be used as an alternative to the more expensive combination including CPT-11 or oxaliplatin.*

Keyword: *5-fluorouracil, Mitomycin-C, Colorectal cancer*

J Med Assoc Thai 2006; 89 (11): 1885-9
Full text. e-Journal: *http://www.medassocthai.org/journal*

5-Fluorouracil (5-FU) has established single-agent activity in advanced colorectal cancer. Its main intracellular target is thymidine synthase, which is inhibited by the active metabolite of 5-FU, 5-fluoro-deoxyuridine monophosphate (FdUMP). The lack of alternative agents until recent years has fuelled extensive research into the biomedical modulation of 5-FU and alternative methods of delivery, primarily based on continuous infusion of the drug[1].

Mitomycin-C (MMC) has been in use for the treatment of metastatic colorectal cancer for many years with a response rate of 0-30%. In a multicenter randomized trial including 200 patients with chemotherapy-na ve disease, the addition of MMC to a protracted venous infusion of 5-FU improved the response rate (54% vs 38%, p = 0.024), and median failure-free survival (7.9 vs 5.4 months, p = 0.033) compared to protracted venous infusion 5-FU alone[2].

Since 1993, the authors have used 5-FU and MMC as a standard regimen for all patients with colorectal cancer. During the recent years, many clinical studies demonstrated the advantages of two new drugs (CPT-11 and oxaliplatin) over the old regimen. However, there were also some limitations, particularly the cost of treatment. Because of Thailand's economical status, the search for alternative regimens of low cost and toxicity must be encouraged.

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Material and Method

Between January 1993 and December 2000, 1083 patients with colorectal cancer were treated at Department of Surgery, Srinagarind Hospital. All patients got radical colorectal resection. Among these, 559 patients with advanced colorectal cancer were reviewed and divided into 2 groups: 121 patients with chemotherapy (chemotherapy group, CG) and 438

patients without chemotherapy (non-chemotherapy group, NCG). The chemotherapeutic regimen consisted of bolus MMC (10 mg/m^2) on first day, 5-FU (600 mg/m^2/day) was given as a continuous infusion for 5 days, repeated every 4 weeks, 6 cycles.

Toxicity was classified according to World Health Organization (WHO) criteria into grades 1-4[3]. At the 3rd and 6th cycles, ultrasonography of the liver and abdomen and X-rays of the lungs was performed to check for metastasis. At each cycle, serum plasma levels of the liver enzymes, bilirubin, electrolytes, CBC and tumor markers carcinoembryonic antigen (CEA) were determined. In 40 patients with liver metastasis, computed tomography (CT) scan with and without intravenous contrast medium was performed to determine hepatic response, instead of ultrasonography.

Hepatic response was determined according to WHO criteria[3]. The sum of the products from the two maximal perpendicular dimensions of each reference lesion was calculated, and the results were compared with the initial CT scan performed preoperatively. A complete remission (CR) had occurred, if all signs of hepatic metastases had resolved. If the sum of the products was decreased by greater than or equal to 50% compared with the initial CT scan, this was counted as partial remission (PR). The intrahepatic disease status was evaluated by not greater than 24%. If the increase was greater than or equal to 25% or in case new liver metastases were detected, a disease progression (PD) would have occurred. The response, calculated for each patient, was the best achieved response in comparison to the status prior to treatment.

Statistical analysis was performed with WinSTATA version 6.0 software. The median survival time and the survival rates were analyzed according to Kaplan-Meier methodology. Wilcoxon Sign-Rank test was used to evaluate the treatment arms. A p-value of less than 0.05 was considered statistically significant.

Results

Among 559 patients, 346 patients were males and 213 patients were females. The mean age was 52 years. The ratio of colon and rectal cancer was 1.02 (Table 1). Nearly all patients (88.89%) in CG had tumors with moderate differentiation, while half of the NCG had the histology as shown in Table 2.

The median survival was significantly increased ($p < 0.001$) for patients in CG (13.17 months, 95%CI 9.46-16.88) compared to NCG (4.43 months, 95%CI 4.32-4.54). Overall survival was demonstrated as Kaplan-Meier survival curves (Fig. 1). In such

Table 1. Patient characteristics

Characteristic	Patients (n = 559)	
	Chemotherapy group	Non-chemotherapy group
Number	121	438
Mean age (years)	50	55
Sex (M:F)*	70:51	276:162
Site (C:R)**	44:77	238:200

* M = male, F = female
** C = colon, R = rectum

Table 2. Histological differentiation

	Patients (%)	
Histology	Chemotherapy group	Non-chemotherapy group
Well	5.56	42.01
Moderate	88.89	50.91
Poor	5.56	5.94
Unknown	6.94	0

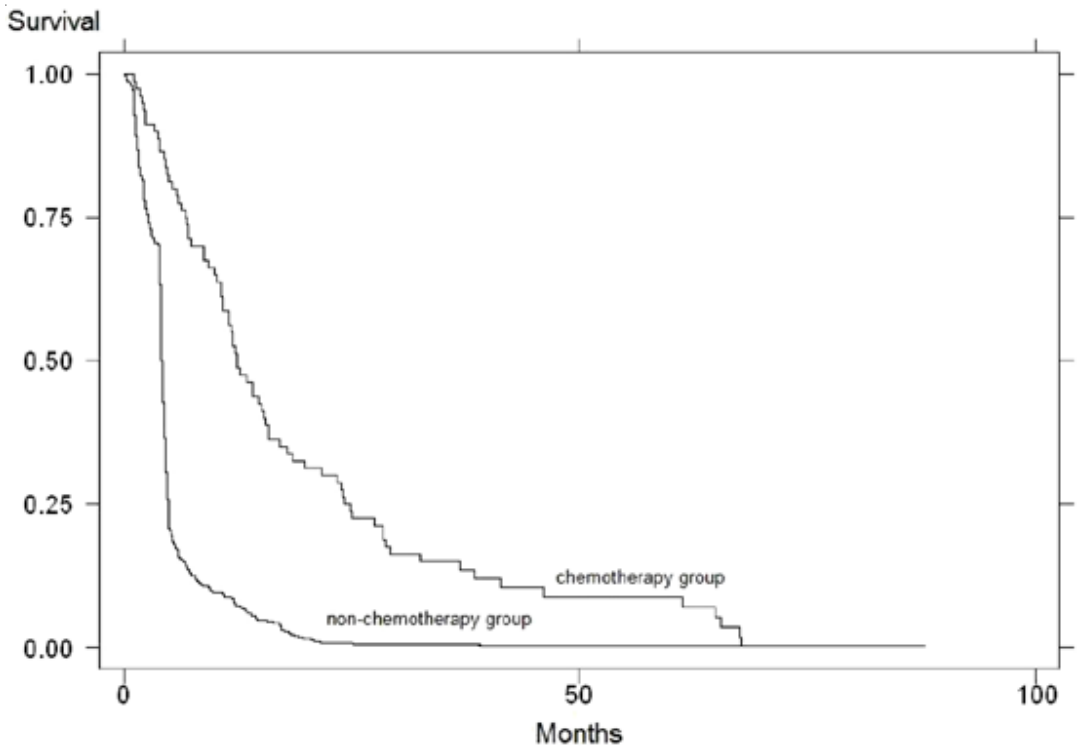

Fig. 1 Kaplan-Meier survival curve for all 559 patients

cases, the patients' death was checked from population registry database at Ministry of Internal Affairs.

Among all the 40 patients with liver metastasis evaluated by radiological response, they induced an overall (best) response rate of 45% (95%CI 35.4-54.6) with a CR in 3 (7.5%) and PR in 15 (37.5%). No change was noted in 9 (22.5%) and intrahepatic PD in 13 (32.5%).

The most frequent side effects were hematologic, followed by gastrointestinal toxicities (Table 3). No treatment-related death was reported. When toxicity grade 3-4 occurred, the chemotherapy would be postponed for 1-2 cycles until the toxicity resolved to normal.

Table 3. Toxicities

Toxicity	Grade 1-2	Grade 3-4
Mucositis	21	1
Nausea / Vomiting	65	1
Leucopenia	68	14
Thrombocytopenia	28	11
Anemia	70	8
Infection	30	1

The cost of 6 cycles of this chemotherapy in the Srinagarind Hospital setting was calculated assuming that no complication occurred. The treatment was done on an inpatient basis. Such cost could be estimated to be 90-110 US$/cycle. This might be compared to the new regimen of 5-FU and CPT-11 where the cost for the same length of treatment was 12 times higher[4].

Discussion

The authors' department, all patients with colorectal cancer had usually been offered chemotherapy after radical resection of the primary site. Unfortunately, only one-fourth of advanced cases received it, because patients or their relatives had refused any treatment after radical resection. Some patients believed that a colostomy always indicated poor prognosis and there was no need to treat anymore. Malnutrition, which was one of the most common problems in this area, affected many patients to develop toxicity easily or recover slowly. Long distances from the hospital, diffi-

cult transportation, poor economic status, and insufficient family support might have contributed to the high rate of loss to follow-up.

Regimen of 5-FU and MMC was proven superior to regimens of 5-FU and leucovorin or cisplatin or methotrexate in advanced colorectal cancer[2,5,6]. Because of higher toxicity, this regimen was less popular than 5-FU and leucovorin. Leucovorin was available at Khon Kaen University Hospital in 1998, but the authors did not change the regimen because of acceptable toxicity of MMC and higher cost of leucovorin. Sobrero A et al[7] reported regimen of 5-FU modulated by leucovorin, methotrexate, and mitomycin which resulted in longer median survival time (18.8 months) than the present study (13.1 months), but higher grade 3-4 toxicity (14.56% vs 11.64%).

With the aim to reduce toxicity, UFT and MMC were used to replace the standard 5-FU and MMC. Many clinical studies have been conducted to evaluate their efficacy[8,9]. However, the results have been controversial in proving a significant improvement in the disease-free interval and/or patient survival rate after surgery. Moreover, carcinoma recurrence and metachronous metastasis occasionally occurred even during adjuvant chemotherapy, particularly liver metastasis, and pelvic recurrence[10,11]. In a study measuring the serum level of 5-FU in patients with oral tegafur or UFT , minimal serum levels were maintained in about 75% of the patients, even though regular administration was in accordance with the prescription[12].

Limitation of the present study was retrospective non-randomized design, which might not conclude the result. Even with a very highly significant value, some biases could affect these differences. A prospective randomized trial should be performed to confirm the present result.

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5-fluorouracil และ *mitomycin-C*: สูตรยาเคมีบำบัดที่มีประสิทธิภาพและราคาถูก สำหรับผู้ป่วยมะเร็งลำไส้ใหญ่และทวารหนัก

พจน์ชวิทย์ อภินิเวศ, วัชรพงศ์ พุทธิสวัสดิ์, โอวตือ แซ่เซียว, ทองอวบ อุตรวิเชียร

วัตถุประสงค์: *เพื่อประเมินประสิทธิภาพของสูตรยาเคมีบำบัด 5-fluorouracil (5-FU) และ mitomycin-C (MMC) ในการรักษามะเร็งลำไส้ใหญ่และทวารหนักระยะแพร่กระจาย*

วัสดุและวิธีการ: *ผู้ป่วยมะเร็งลำไส้ใหญ่และทวารหนักระยะแพร่กระจายที่ได้รับการผ่าตัด ระหว่างเดือน มกราคม พ.ศ. 2536 ถึง ธันวาคม พ.ศ. 2543 จำนวน 559 คน ได้รับยาเคมีบำบัดหลังการผ่าตัดจำนวน 121 คน สูตรยาที่ใช้ คือ MMC 10 มก./ตร.ม. ในวันแรก และ 5-FU 600 มก./ตร.ม./วัน ทางเส้นเลือดดำ เป็นเวลา 5 วัน ให้ทั้งหมด 6 ครั้ง ทุก 4 สัปดาห์ ประเมินผลข้างเคียงและประสิทธิภาพของยาตามเกณฑ์ขององค์การอนามัยโลก และประเมินอัตรารอดชีพตามวิธีการ Kaplan-Meier*

ผลการศึกษา: *ผู้ป่วยที่ได้รับยาเคมีบำบัด หลังการผ่าตัดรักษา จำนวน 121 คน ประกอบด้วยผู้ชาย 70 คน และผู้หญิง 51 คน อายุเฉลี่ย 52 ปี สัดส่วนระหว่างมะเร็งลำไส้ใหญ่และทวารหนักเท่ากับ 0.57 พบก้อนมะเร็งกระจายไปตับในผู้ป่วยจำนวน 40 คน แสดงผลการตอบสนองต่อยาเคมีบำบัด ร้อยละ 45 แบ่งเป็นผู้ป่วยที่มีการตอบสนองอย่างสมบูรณ์ ร้อยละ 7.5 และมีการตอบสนองบางส่วน ร้อยละ 37.5 อัตรารอดชีพเฉลี่ยเท่ากับ 13.1 เดือน ผู้ป่วยสามารถทนต่อผลข้างเคียงของสูตรยานี้ได้ดี โดยพบผลข้างเคียงระดับ 3-4 เพียงร้อยละ 11.64*

สรุป: *การศึกษานี้แสดงว่าสูตรยาเคมีบำบัดนี้ที่ประกอบด้วยยารุ่นเก่า มีประสิทธิภาพดี ผลข้างเคียงยอมรับได้ และราคาประหยัด สามารถใช้แทนสูตรยาเคมีบำบัดที่ประกอบด้วยยารุ่นใหม่ แต่มีราคาแพงได้*