Original Article

Weekly Regimen of Low-Dose 5-Fluorouracil and Leucovorin as Adjuvant Chemotherapy for Colorectal Cancer

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Key Words
Colorectal cancer;
Chemoradiation;
Adjuvant chemotherapy

Background. The aim of this study is to present the experiences in our institution on adjuvant chemotherapy or chemoradiation for patients suffering stage III colorectal cancer.
Methods. One hundred twenty patients between March 1998 and March 2006 who underwent one-stage surgery were subsequently put under a weekly regimen of 5-FU at 500 mg/m2 with LV at flat 100mg for 24 times. Among them, thirty nine patients received concurrent long-course radiation with total dosage of 5040cGy. Eighty-nine patients that completed chemotherapy or chemoradiation were enrolled in the survival analysis.
Results. Three-year OS and DFS rates were 75.19% and 59.63%. Five-year OS and DFS rates were 59.63% and 48.5%, respectively. Total toxicity rate on grade 3 and 4 was mainly due to radiation proctitis in 15.38% patients. One (0.83%) patient suffered febrile neutropenia. The grade 1 or 2 toxicity were mainly from fatigue in 18.33% patients, nausea/anorexia in 4.17%, diarrhea in 19.17% patients as well as stomatitis/mucositis in 5.0% patients. Clinical physicians' practice was responsible toxicity for 9.1% of patients, including one Port-A-related right arm deep vein thrombosis.
Conclusion. Weekly treatment at these doses was convenient and tolerable for the majority of patients, even with concurrent radiotherapy treatment protocol.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2008;19:1-8*]

Colorectal cancer is one of the most commonly diagnosed cancers throughout the world; 40 to 50 percent of colorectal cancer patients who undergo curative surgery alone ultimately relapse and die of metastasis.[1] The presentation that postoperative adjuvant treatment with 5-fluorouracil(5-FU) and levamisole reduced the mortality rate by 33 percent among patients with stage III colon cancer[2] prompted several trials. For over fifteen years, six month treatment with systemic adjuvant 5-FU plus leucovorin (LV) has been a standard protocol for stage III colorectal cancer.[3-6]

We retrospectively report the long-term results of post-operative adjuvant chemotherapy with or without radiotherapy in our institute by applying outpatient protocol involving weekly bolus 5FU-based regimen.

Received: August 10, 2007. Accepted: February 4, 2008.
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Methods

Patients

Since February 1998 to February 2006, patients who received colorectal cancer surgery at our institution were subsequently prescribed once-weekly bolus 5-FU plus LV for 24 times.

The inclusion criteria was fitness as judged by their physicians for starting full-dose chemotherapy within two months of surgery, and radiotherapy completed within four months of surgery. All patients received one-stage surgery.

The exclusion criteria was defined as (1) patients who did not undergo their operation at our institute. (2) Patients who did not receive one-stage surgery. (3) Patients' pathology report did not present clear distal margin. (4) Patients did not complete the chemotherapy course at our institute due to patients' compliance issues (e.g. traffic, facility and referral to other hospital). (5) Patients ended up entering other clinical trials. (6) Patients who received pre-operation concurrent chemoradiation. (7) Patients who changed protocol not based on the toxicity (e.g. some patients who accepted weekly bolus 5-FU only shifted to 5-FU/LV between 1997 to 1998; or shifted to QUASAR2 regimen[7] after 2006. (8) Patients who failed to be followed up or seek other treatment protocol (e.g. oral chemotherapy).

Regiment

All treatment was conducted by an appropriately trained nurse in a chemotherapy clinic. A flat-rate 100 mg dose of leucovorin, regardless of patient body-surface- area, was given as a slow intravenous injection more over 5 minutes. This was followed by 5-FU at 500 mg/m2, also given over 5 minutes. Routine prophylactic antiemetics were not used. The total planned treatment duration was 24 weeks. Doses omitted for toxicity or patient-related issues (e.g. holidays) during this period were routinely added on at the end of the planned treatment duration to complete the 24 injection schedule.

For rectal cancer patients, concurrent radiotherapy was suggested and given with patient's consent (e.g. traffic, facility). Radiotherapy involving pelvic irradiation was given as a total dose of 5040cGy in 28 fractions over 5.5 weeks. Radiotherapy was delivered with 10MV or 15MV photon beams using three-field belly board technique or three-dimensional conformal radiotherapy (3DCRT).

Monitoring of toxicity was performed by clinical physicians, and omitted if more than third grade toxicity shown until recovery, or with a dose-reduction of 10-25% at the discretion of the responsible physician.

Data

These patients' chart was examined again. Medical records were reviewed and toxicity was recorded in a standardized manner by applying the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and Radiation Therapy Oncology Group (RTOG) acute radiation morbidity scoring criteria.[8,9] The tumor stage was based on American Joint Committee on Cancer (AJCC) TNM Stage.[10]

Statistics

Patient characteristics and toxicity evaluation were calculated using a Microsoft Excel® spreadsheet.

A statistical software package (SPSS®, Chicago, IL) was used for evaluating survival based on the Kaplan-Meier method and log-rank analysis. The survival analysis was for patients who completed the course.

Results

Patient characteristics

During March 1998 and March 2006, there were 120 patients identified as having undergone one-stage surgery and subsequently administered the weekly regimen of 5-FU at 500 mg/m2 with LV at flat 100mg for 24 times. Of these, 39 patients received concurrent long-course radiation. The patient characteristics are listed in Table 1.

Of the 120 patients, 89 patients (73.6%) completed the chemotherapy or chemoradiation course. Among the 32 patients who failed the complete protocol, six of them were noted with progressive disease

Table 1. Patient characteristics

Age	
Mean (95% CI) (yr)	60.2 (57.8-62.6)
≥ 70 years (%)	25%
Sex	
Male:Female	56.7%:43.4%
BSA	
Mean (95% CI)	1.64 (1.61-1.68)
Preceding surgery	
Right hemicolectomy	13.3%
Left hemicolectomy	3.3%
LAR	72.5%
APR	5.0%
Hartmann's operation	1.5%
Subtotal/Total colectomy	3.3%
LN harvest	
Mean (95% CI) (n)	17.5 (15.4-19.6)
Tumor stage	
IIIA	10%
IIIB	50%
IIIC	40%
Carcinoembryonic antigen	
≤ ULM*	50.83%
> ULM	40.83%
missing data	8.33%
Total number	120

*ULM: normal range ≤ 5ng/mL.

and shifted to other treatment approaches; there were eleven complications (9.1%), including four radiation proctitis, four grade three diarrhea, one grade four diarrhea related sepsis, one neutropenia fever, and one patient with Port-A device induced right-arm deep vein thrombosis. There were another four patients with other underlying disease and dropped out the study, including one urethral stone induced urosepsis, one unstable angina, one pulmonary T.B., one schizophrenia patient without co-operation. Other patients (9.1%) refused for personal reasons.

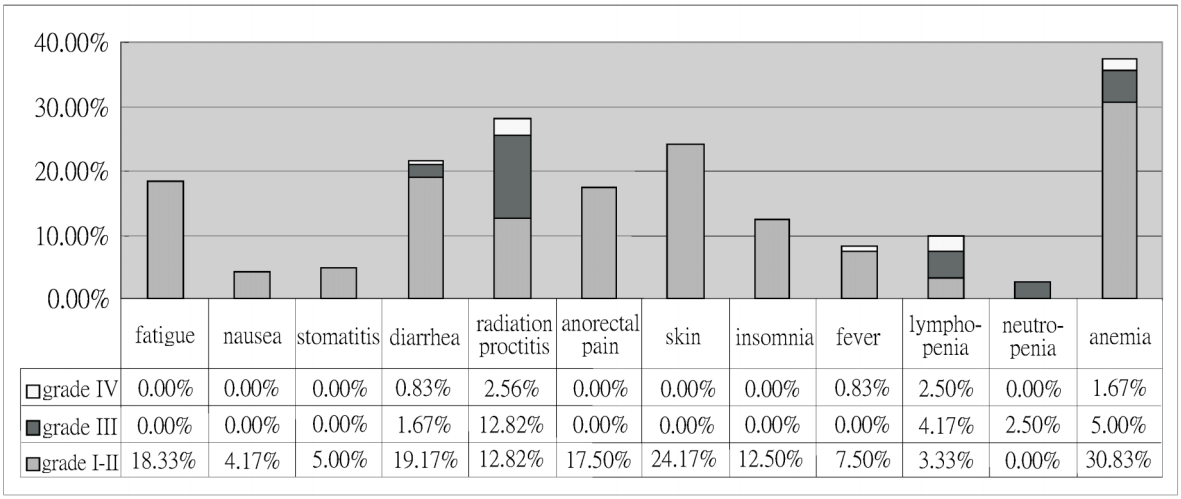
The mean follow-up duration for all patients was 37.81 months (95% C.I. 26.20-43.54 months). The follow-up protocol at our hospital is similar to the National Comprehensive Cancer Network Clinical Practice Guideline in Oncology for rectal cancer.[11]

The mean lead time from surgery to chemoradiation was 26.49 days (95% C.I. 20.16-28.25 days). Of the 39 patients who accepted concurrent radiation, the mean difference in starting time between chemotherapy and radiation was 5.1 days (95% C.I. 3.56-6.65 days; median 4.0 days).

Toxicity, dose reduction, stoppages and delays

Treatment was generally well tolerated. The dosage reduction was not found. Most patients completed the regimen within six months, except for 19 patient (15.8%) that were put on hold once for personal reasons. There were four patient (3.3%) put on rest for one month due to toxicity. In total there were 11 patients (9.1%) were put on hold for toxicity.

The toxicity grading is listed in Fig. 1. There was one patient (0.83%), who was concurrently subject to radiation therapy, that suffered from neutropenic fever. One patient was noted to have grade III neutropenia; Another one patient was noted to have life-threatening diarrhea. All three patients (2.5%)



	fatigue	nausea	stomatitis	diarrhea	radiation proctitis	anorectal pain	skin	insomnia	fever	lympho-penia	neutro-penia	anemia
grade IV	0.00%	0.00%	0.00%	0.83%	2.56%	0.00%	0.00%	0.00%	0.83%	2.50%	0.00%	1.67%
grade III	0.00%	0.00%	0.00%	1.67%	12.82%	0.00%	0.00%	0.00%	0.00%	4.17%	2.50%	5.00%
grade I-II	18.33%	4.17%	5.00%	19.17%	12.82%	17.50%	24.17%	12.50%	7.50%	3.33%	0.00%	30.83%

Fig. 1. chemotherapy toxicity: All are based on NCI toxicity except for acute radiation proctitis is based on RTOG.

were found to have grade II radiation proctitis.

One Port-A catheter- related right arm deep vein thrombosis (DVT) was also noted.

For patients who received concurrent radiation, radiation proctitis was commonly found. There was one (2.56%) grade 4 proctitis that required blood transfusion for LGI bleeding. The RTOG grade 3 proctitis was noted in five patients (12.82%), and two of them suffered from retro-rectal abscess that needed surgical intervention.

Survival

Eighty-nine patients completed the chemotherapy or chemoradiations were enrolled to survival analysis.

Three-year and five-year OS rates were 75.19% and 59.63% respectively. The three-year and five-year DFS rates were 61.31% and 48.5% respectively.

The subgroup was further divided into colon and rectum for analysis. There were 57 colon cancer patients and 33 rectal cancer patients.

For the colon group, the three-year and five-year OS rates were 79.57% and 61.75% respectively. The three-year and five-year DFS rates were 59.16% and 49.94% respectively. (Figs. 2 and 3)

For the rectum group, the three-year and five-year OS rates were 61.83% and 50.25% respectively. The three-year and five-year DFS rates were 69.87% and 34.48% respectively. (Figs. 2 and 3)

When stage was further focused on survival analysis, there were nine, forty two, thirty eight patients

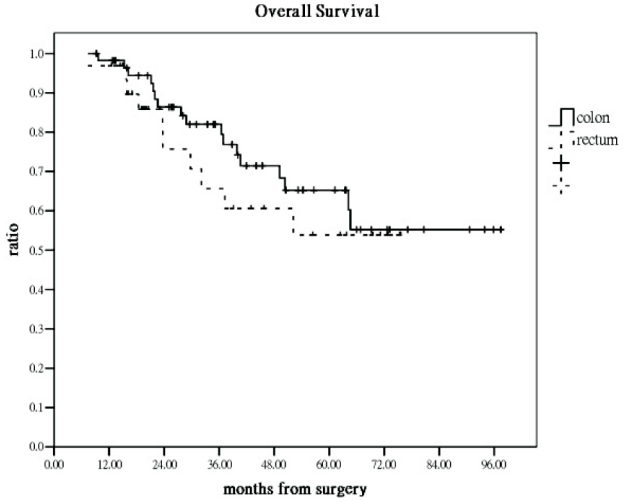


Fig. 2. Overall survival rate.

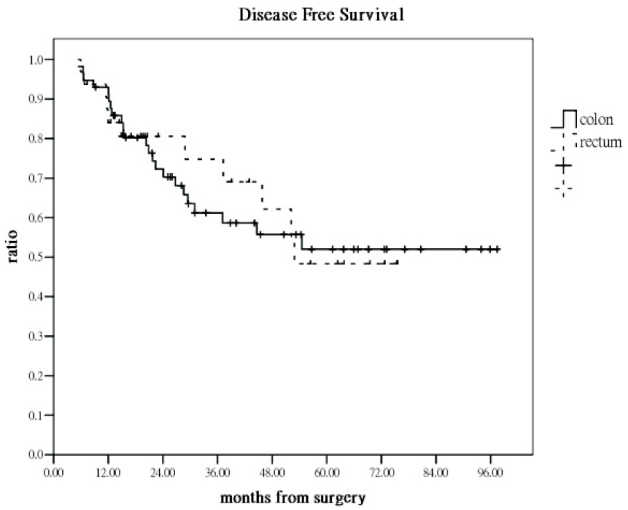


Fig. 3. Disease free survival rate.

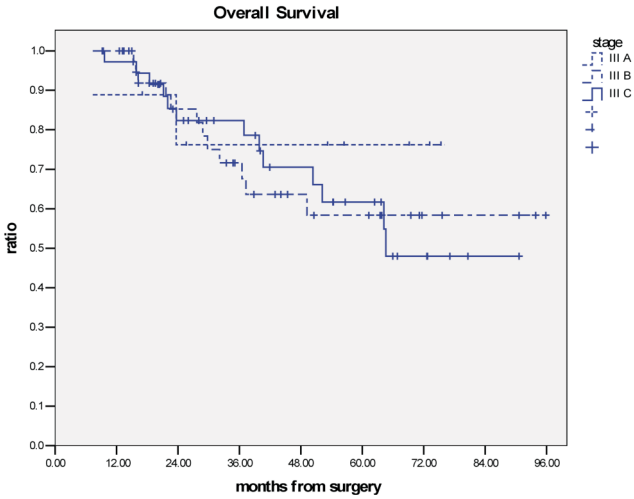


Fig. 4. Overall survival rate for stage.

for stage III_A, III_B, III_C.

Due to the limited number of studied population, the OS for stage III_A was 76.2% after 2 year, and the DFS was 77.8% after 1 year. The three-year OS and DFS rate were 68.06%, 56.45% for stage III_B, and 78.86%, 58.57% for stage III_C. The five-year OS and DFS rate were 53.6%, 45.4% for stage III_B, and 58.4%, 43.3% for stage III_C (Figs. 4 and 5).

Discussion

Systemic adjuvant 5-FU-based chemotherapy has been the standard treatment approach after resection

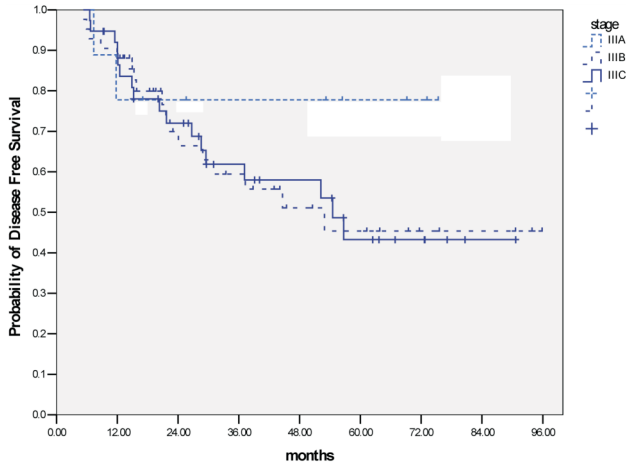


Fig. 5. Disease free survival rate for stage.

of stage III colon cancer in suitable patients.[2,3,5,6,12] To combine the radiation for stage II and III rectal cancer has also been a standardized protocol.[5,6,12-14]

At present, the best recognized chemotherapy regimen in adjuvant colorectal cancer treatment is the 4-week Mayo Clinic schedule,[15] the weekly Roswell Park regimen,[16] IMPACT (Machover regimen),[4] the QUASAR regimen,[7,17] daily oral UFT,[18] and Xeloda.[19] The new advice was proved after MOSAIC study for the FOLFOX4 regimen.[20]

The Mayo Clinic schedule calls for of 425mg/m2 bolus 5-FU plus 20mg/m2 LV daily for 5 days, repeated every 4-5 weeks for six cycles. It is the first famous protocol and was proven superior to other regimens in the large US Intergroup trial INT-0089.[21] But it caused high toxicity, with up to 36% grade 3-4 mucositis, 24% grade 3-4 diarrhea, 24% neutropenia. A recent retrospective review by Tomiak et al.[22] highlighted the problems of administering the Mayo Clinic schedule in routine clinical practice, with 35% of patients not receiving even the second cycle of treatment as planned because of toxicity.

The Machover regimen (IMPACT study) is like the Mayo regimen as it is given over five consecutive days each month, but uses a lower dose of 5-FU (370-400 mg/m2) with a higher dose of LV (200 mg/m2). However, 26% of patients treated with this regimen still experienced grade 3 or 4 toxicity.[23]

The weekly Roswell Park regimen was superior to previous version; it involves 6 weekly treatment of 5-FU at 500 mg/m2 with high-dose LV (500 mg/m2), followed by 2 weeks rest, for six cycles (48 weeks). But the toxicity remains high, produced grade 3 or 4 toxicity in 28% patients.[16]

The large UK-based trial, QUASAR, has been important in identifying simple but better-tolerated regimens for bolus 5-FU and LV. It reduced the grade 3 or 4 toxicity to below 20% of patients, with 35% of patients needed dose reductions while achieving 84% completion rate. The new regimen of QUASAR is a weekly set of bolus 5-FU at 425 mg/m2 with LV (flat 45 mg).

Oral UFT (NSABP C-06 study) and Xeloda (X-ACT study) has been proven to be a safer profile. There is less neutropenia and infrequent diarrhea as noted in UFT. Xeloda also offers less toxicity, with only 0.3% febrile neutropenia, and less than 10% of grade 3 or 4 toxicity, though higher hand-foot syndrome can be as high as 62%.[24]

In our regimen, the grade 3 or 4 toxicity totalled 47.88%, mainly from radiation proctitis in 15.38% of patients and diarrhea in 15.67% of patients. One (0.83%) patient suffered from febrile neutropenia. Other patients had less toxicity. The grade 1 or 2 toxicity were mainly from fatigue in 50.83% of patients, nausea/anorexia in 45.83%, diarrhea in 22.5%, and stomatitis/mucositis in 22.5%. We noticed that only the incidence of fatigue was higher than other trials and there was a high ratio of anemia as well, with 30.83% grade 1 or 2 and 37.5% in all patients. Nevertheless, it may be a false appearance because the low incidence of neutropenia/lymphopenia and none of the thrombocytopenia was found in light of suppressed bone marrow.

When the grade 3 or 4 toxicity was noted, the clinical physicians in our institute held up chemotherapy once for observation and management. In this retrospective study, we did not conduct any dosage reduction. There was a total of 19.1% patients put on rest for more than one time, and 9.1% dropped out the treatment due to toxicity. The toxicity related disruption of treatment is less than Mayo, IMPACT, QUASAR protocol but cannot be compared against UFT or Xeloda.

The survival analysis is similar to other regimen. The three-year DFS is 61.31% and the five-year OS is 59.63%. But the limited case number made it impossi-

Table 2. Options for adjuvant treatment in colorectal cancer, comparison

	Survival	Toxicity
Mayo	5-year DFS 60% 5-year OS 66%	36% grade 3-4 mucositis, 24% grade 3-4 diarrhea, 24% neutropenia. 35% not accept even the 2nd course.
IMPACT (Machover)	3-year DFS 71% 3-year OS 83%	26% grade 3 or 4 toxicity
Roswell Park	5-year DFS 58% 5-year OS 66%	28% grade 3-4 toxicity
QUASAR	3-year OS 70.6%	11% diarrhea 6% nausea/vomiting
MOSAIC (FOLFOX4)	4-year DFS 76.4% OS 84.3%	12% grade 3 neuropathy
UFT	5-year OS 78.7% 5-year DFS 66.9%	well tolerated
Xeloda	3-year OS 81.3% 3-year DFS 64.2%	62% hand-foot syndrome
This study	3-year DFS 61.31% 5-year OS 59.63%	15.38% grade 3-4 radiation proctitis 15.67% grade 3-4 diarrhea 0.83% febrile neutropenia

ble for further meta-analysis with other regimen. The comparison summary is listed in Table 2.

Recently, positive results from the international MOSAIC (Multi-center International Study of Oxaliplatin/5-FU/Leucovorin in the Adjuvant Treatment of Colon Cancer) trial were reported.[23,25] The three-year DFS was up to 77.8%. There was also a 23% risk reduction. However, 12.4% grade 3 neuropathy was also noted. This heralds another new era and window for the adjuvant therapy of colorectal cancer.

Conclusion

We reported our experience and long-term result of this regimen. Weekly treatment at these doses is convenient and well-tolerated for the majority of patients, even with concurrent radiotherapy.

Acknowledgements

We thank Ms. Huei-huei Lin, Pei-jung Chi and the Cancer Registry and Tumor Center, the Coding Division of Medical Record Department and the Information System Department of CCH in data collection. We apologize to any colleagues whose work was not cited because of content limitations or oversight on our part.

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原　著

每週一次注射低劑量 5FU 及葉酸為第三期大腸直腸癌患者輔助化學治療的長期追踪報告

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目的　我們在此報告本院第三期大腸直腸癌的患者在手術後，接受輔助化學治療或化學放射治療所使用的處方及其成效。

方法　自西元 1998 年 3 月至 2006 年 3 月，共有 120 位常規手術患者，手術後接受每週一次門診注射化學針劑，使用藥物為 5-FU 500 mg/m^2 及葉酸 100 mg。其中 39 位病人同步接受五週半、總劑量 5040cGy 的放射治療。共 89 位病人完成治療者納入存活率之計算。

結果　三年存活率及三年無疾病存活率是 75.19%、59.63%。五年存活率及五年無疾病存活率分別是 59.63%、48.5%。三級以上的毒性反應主要是放射性直腸炎 15.38% 及一位病人有發燒性嗜中性白血球低下症。二級以下的毒性反應主要是疲累感 18.33%、噁心厭食 4.17%、腹瀉 19.17%、口腔破皮或胃發炎 5.0%。因為毒性反應造成治療中斷佔 9.1%，其中包含一位因人工靜脈血管造成右上臂和右頸靜脈深部靜脈栓塞。

結論　對於大部分的患者而言，既使在合併放射治療下，此方法仍是有效且毒性是可以忍受的。

關鍵詞　大腸直腸癌、化學放射治療、輔助化學治療。