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Uracil-Tegafur and Leucovorin is an Effective Alternative Adjuvant Chemotherapy for the Patients with Colorectal Cancer—Extend Period of Treatment Might Prolong Patient's Survival

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Keywords:

Uracil-futraful; Leucovorin; Colorectal cancer; Adjuvant chemotherapy; Diarrhea

1. Abstract

1.1. Background: Adjuvant chemotherapy is recommended for patients with colon cancer in stage III and stage II accompanied with high-risk features. The study is to clarify effects of oral adjuvant chemotherapy of uracil-futraful (UFUR) and leucovorin on Dukes B and Dukes C colorectal cancer (CRC) patients.

1.2. Methods: CRC patients receiving surgery and chemotherapy from March 2005 to October 2013 were enrolled. End of follow up was October 2020 or upon mortality. The patient's status of performance was from 0-2. The patients who were lost in follow up, didn't finish the chemotherapy were excluded. A p-value of less than 0.05 was considered statistically significant.

1.3. Results: 127 patients received 400 mg UFUR and 60 mg leucovorin daily for 2 years; 245 patients for 1.5 years; 59 patients for 1 year. No grade 3 or 4 toxicity occurred. No patients suffered from febrile neutropenia. The grade 1 or 2 toxicity was mainly due to diarrhea in 57 patients (11.6%), fatigue in 52 patients (10.5%), nausea/anorexia in 15 patients (3.1%), and stomatitis/mucositis in 12 patients (2.4%). The low incidence of neutropenia/lymphopenia in 63 patients (12.8%) and thrombocytopenia in 65 patients (13.2%) (Table 2). Patients with UFUR and leucovorin for 2 years had better survival than those who were with for 1.5 years and 1 year respectively

1.4. Conclusion: UFUR/ leucovorin may replace 5-FU in the adjuvant setting because of its effectiveness, safety with less side effects and equivalent. OS, avoid complication of central venous catheter, reduced hospitalization and cost, and more freedom for the patients. Patients should be encouraged to take medications for 2 years as adjuvant chemotherapy for CRC following surgical resection.

2. Mini-Abstract

UFUR/ leucovorin may replace 5-FU in adjuvant setting because of effectiveness, safety and equivalent OS, Patients should be encouraged to take medications for 2 years for CRC following surgical resection.

3. Background

Colorectal cancer (CRC) is the most common cancer in Taiwan and the third leading cause of cancer-related mortality [1]. In 1992, the National Institutes of Health published the first evidence-based guideline for using adjuvant therapy among patients with colorectal cancer [2]. Multiple randomized trials also showed reduced incidence of death and disease recurrence in patients with stage III colon cancer treated using adjuvant chemotherapy [3,4]. The peer-review group determined that patients with stage III colon cancer can benefit from adjuvant fluorouracil (5-FU)-based chemotherapy [5]. In patients with non-metastatic CRC, the status of lymph node metastasis is the strongest pathologic factor influencing their survival [6]. The five-year survival rate of CRC patients is about 80–85% in stage

I and 70%-75% in stage II [7]. In contrast, only 45% of stage III CRC patients undergo surgery alone [8]; therefore, adjuvant chemotherapy is recommended for colon cancer patients at stage III and stage II accompanied with high- risk features [9]. However, only 50% of such patients in advanced ages undergo adjuvant therapy after surgical resection. The optimal therapeutic strategies in this group of patients must balance the risks and benefits of treatment. Owing to prolonged life expectancy, patients around 70 and 80 years of age require an improved therapeutic plan for this potentially curable disease [10-12]. We aimed to clarify the effects of oral adjuvant chemotherapy of uracil-futraful (UFUR) and leucovorin on stage II (Dukes B) and stage III (Dukes C) CRC patients.

4. Materials and Methods

CRC patients with and without lymph node metastasis receiving surgery and chemotherapy under the care of the senior author TCH from March 2005 to October 2013 were enrolled. End of follow up was October 2020 or upon mortality. The patients selected to participate in the present study were aged ≥18 years and exhibited histologically determined CRC. The stage of CRC was either Stage III (Dukes' C) or Stage II (Dukes' B) with high risk of recurrence and metastasis. High risk stage II included patients with vascular, lymphatic, or perineural invasion in the surgical specimen. Prior to study enrollment, the following inclusion criteria were determined: a Karnofsky performance status of ≥80%, ≤2.0 mg/dL bilirubin, ≤1.5 mg/dL creatinine, an absolute granulocyte count of ≥1500/μL, and a platelet count of ≥100,000/μL.

In the present study, all enrolled patients were treated with continuous UFUR (300 mg/m2/day) and leucovorin (45–60 mg/m2/day). Each UFUR capsule (TTY BioPharm, Co., Ltd., Taipei, Taiwan) contained a 1:4 molar ratio of the 5 fluorouracil (5 FU) prodrug tegafur (100 mg) and the dihydropyrimidine dehydrogenase inhibitor uracil (224 mg). Each leucovorin tablet (TTY BioPharm, Co., Ltd.) contained 15 mg of leucovorin. The supportive care included loperamide, antiemetic agents, and oral cephradine for diarrhea lasting >48 h. National health insurance of Taiwan reimbursed the amount of money for UFUR and leucovorin usage up to 2 years as adjuvant chemotherapy for colorectal cancer. Upon progression, patients were administered an irinotecan-based or oxaliplatin based regimen in addition to UFUR and leucovorin (TEGAFIRI or TEGAFOX); however, agents including bevacizumub and cetaximub were not routinely used because of insufficient funding during the study period. All patients were monitored from March 2005 until December 2020 or death.

All clinical and pathological data were retrieved from computer files and medical records of Mackay Memorial Hospital. The patients' status of performance was 0–2. The patients who were lost to follow-up or did not complete chemotherapy were excluded. The data were collected and analyzed. P-value < 0.05 was considered statistically significant.

5. Results

In total, 491 patients were included in this study (249 male and 242 female). The mean age was 63 years (range: 51–73 years). Primary site of the tumor was the colon in 217 patients (44.2%) and the rectum in 272 patients (55.4%). There were 84 patients with stage II (Dukes' B) tumors and 407 patients with stage III (Dukes' C) tumors. (Table 1). Excluding patients with additional intravenous injection of chemotherapeutic agents, 127 patients were administered 400 mg UFUR and 60 mg leucovorin daily for 2 years; 245 patients were administered 400 mg UFUR and 60 mg leucovorin daily for 1.5 years; 59 patients were administered 400 mg UFUR and 60 mg leucovorin daily for 1 year. Diarrhea was the most frequently observed side effect; however, it was manageable. In our regimen, no grade 3 or 4 toxicity occurred. No patients suffered from febrile neutropenia. The grade 1 or 2 toxicity was mainly due to diarrhea in 57 patients (11.6%), fatigue in 52 patients (10.5%), nausea/anorexia in 15 patients (3.1%), and stomatitis/mucositis in 12 patients (2.4%). The low incidence of neutropenia/lymphopenia in 63 patients (12.8%) and thrombocytopenia in 65 patients (13.2%) was because of suppressed bone marrow (Table 2). Moreover, patients that were administered UFUR and leucovorin for 2 years had better survival than those who were administered UFUR and leucovorin for 1.5 years and 1 year respectively (Figure 1 for stage III and Figure 2 for Stage II).

Table 1: Characteristics of patients

Eligibility of the study	N 491(100%)
Age, median (range)	63 (51–73) y/o
Sex	N (%)
Male	249 (50.7%)
Female	242 (49.3%)
Stage of tumor	N (%)
ll	84 (17.11%)
lll	407 (82.89%)
Location of tumor	N (%)
Cecum	8 (1.63%)

Ascending	55 (11.2%)
Ascending &transverse	1 (0.2%)
Transverse	29 (5.91%)
Transverse &sigmoid	1 (0.2%)
Descending	23 (4.68%)
Sigmoid	100 (20.37%)
Sigmoid& rectum	1 (0.2%)
Rectum	272 (55.4%)
Transverse& rectum	1 (0.2%)
Regimen of chemotherapy	N (%)
UFUR alone2 B.I.D for 2 years	127(25.87%)
UFUR alone2 B.I.D for 1.5 years	245 (49.90%)
UFUR alone2 B.I.D for 1 year	59 (12.02%)
FOLFOX for 6 months followed by UFUR alone2 B.I.D for 1.5 years	8 (1.63%)
Tega FOX for 6 months followed by UFUR alone2 B.I.D for 1.5 years	26 (5.3%)
5-FU for 6 months	26 (5.3%)

Table 2: Side effect of uracil-tegafur and leucovorin

Side effect	Number of patients (N)	Percentage (%)
Diarrhea	57	11.6
Fatigue	52	10.5
Nausea/anorexia	15	3.1
Stomatitis/mucositis	12	2.4
Neutropenia/lymphopenia	63	12.8

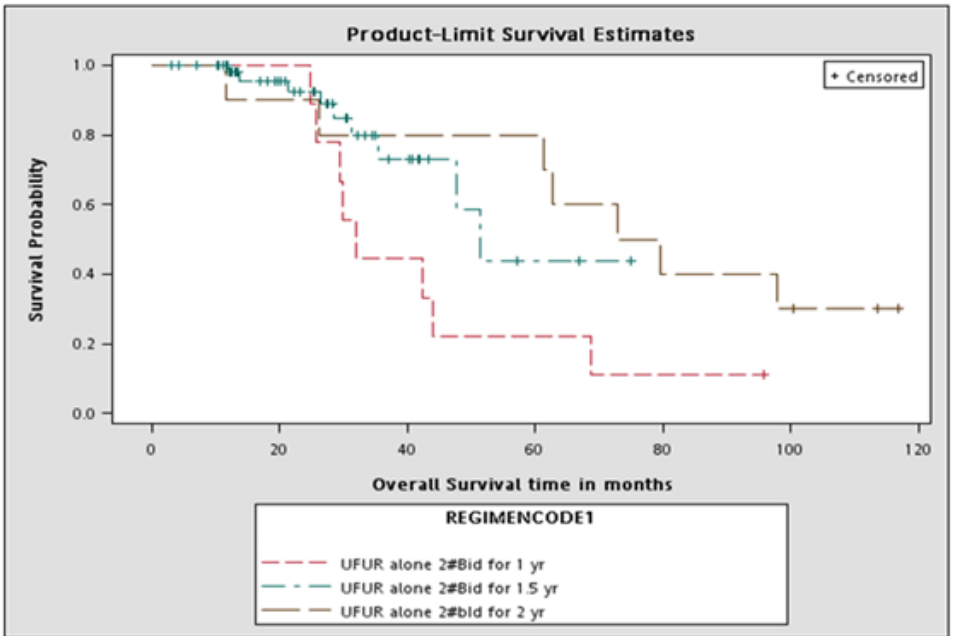

Figure 1:

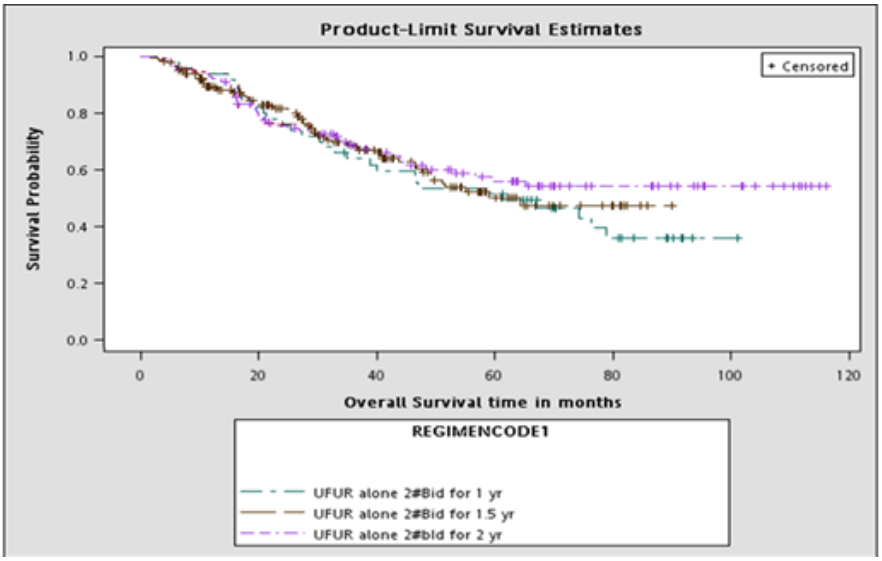

Figure 2:

6. Discussion

Adjuvant chemotherapy with FU and levamisole was recommended for patients with Stage III (Dukes C) colon cancer owing to evidences regarding reduced disease relapse and mortality (30% to 40%) at 5 years [13]. High risk Stage II (Dukes' B) patients could also benefit from adjuvant chemotherapy [7,8]. Although chemotherapy was the standard treatment for stage III (Dukes C) CRC patients, some patients do not follow the guideline owing to advanced age and comorbidities. Therefore, it is important to understand the effect of chemotherapy on overall survival (OS) or disease-free survival (DFS) in clinical practice Although practical implication is important, statistical anlyais is indispensable in most studies. instead of the statistically analysis [14,15]. Most recommended regimens of adjuvant chemotherapy, such as systemic FU plus levamisole or folinic acid, are associated with measureable side effects and subjective symptoms including fatigue, anorexia, loss of taste, and medical dependence, which affect the quality of life, especially among patients with advanced age. Elderly patients are less willing to receive chemotherapy because of their apprehensions regarding the side effects. To ensure appropriate treatment administration, further studies exploring physicians' and patients' knowledge and attitudes toward the treatment are essential.

Currently, optimum chemotherapy regimens in adjuvant CRC treatment is the 4-week mayo clinic schedule, the weekly Rosewell Park regimen, IMPACT (Manchover regimen), and the QUASAR regimen [16]. New advice was proven after MOSAIC study for the FOLFOX4 regimen [17]. The mayo clinic regimen caused high toxicity, with up to 36% grade 3–4 mucositis, 24% grade 3–4 diarrhea, 24% neutropenia [13]. The weekly Rosewell Park regimen had high toxicity; it caused grade 3 or 4 toxicity in 28% patients. However, the limited number of cases made it impossible to conduct further meta-analysis with other regimens [18]. International MOSAIC study reported a six-year DFS rate of up to 78.5%. There was a 23% risk reduction. However, 12.4% of grade 3 neuropathy cases were also noted [18]. These regimens necessitate intravenous injection, which requires insertion of central venous catheter, hospital admission, or carrying an infusor with a small pump that delivers medication for chemotherapy [19]. Oral chemotherapeutic agents such as capicitabine or uraci-futraful are alternatives to chemotherapy, both for adjuvant and metastatic CRC (20). Previously we published a manuscript titled "Pharmacoeconomic analysis of Capecitabine versus 5-Fluorouracil/Leucovorin as adjuvant therapy for stage III colon cancer in Taiwan" in the journal of "Value in Health," to assess the cost-effectiveness of oral capecitabine compared with intravenous bolus 5-fluorouracil/leucovorin (5-FU/LV) in the adjuvant treatment of stage III colon cancer in Taiwan from payer (Bureau of National Health Insurance [BNHI]) perspectives. We found that from the perspectives of the BNHI and society in Taiwan, capecitabine is cost-effective and it also improves health outcomes compared with 5-FU/LV in the adjuvant treatment of stage III colon [21] cancer. We also published an article titled "Cost minimization comparison of oral UFT/L versus 5-FU/LV as adjuvant therapy in the "Journal of Comparative Effectiveness" in the journal of "Research J Comp Effectiveness, to determine the more cost-effective treatment alternative between UFT/LV and 5-FU/LV in Stages II and III CRC from Taiwan's National Health Insurance perspective. In total, US$ 3620.80–$ 3709.16 per patient per treatment were saved during the UFT/LV treatment. UFT/LV had outcomes comparable to those of 5-FU/LV; UFT/LV was also the more cost-effective treatment as adjuvant chemotherapy [22].

Further, owing to a similar survival rate and lower toxicity, oral UFUR/LV is suggested as an alternative regimen to intravenous 5-FU/LV in post-operative CCRT of locally advanced rectal cancer; the data was published in the journal of "Anticancer Research"

as "Post-operative Concurrent Chemoradiation Therapy Using Oral Uracil-tegafur versus Weekly Intravenous Fluorouracil for Locally Advanced Rectal Cancer" [23]. Even among aged patients, radical surgery followed by adjuvant CCRT using oral tegafur was well tolerated and resulted in fair clinical outcomes; our observation (investigation) was published in the "International Journal of Gerontology" as "Radical Proctectomy Followed by Adjuvant Chemoradiation with Oral Tegafur is Well Tolerated by Elderly Patients with Rectal Cancer" [24].

Although oral UFT (NSABP C-06 study) and Xeloda (X-ACT study) have a safer profile, there is less neutropenia and infrequent diarrhea in UFT than in Xeloda. In this retrospective study, the author did not conduct a dosage reduction. Moreover, the low incidence of neutropenia/lymphopenia in 63 patients (12.8%) and thrombocytopenia in 65 patients (13.2%) was attributed to bone marrow suppression. Patients who were administered UFUR and leucovorin for 2 years showed better survival than those who were administered UFUR and leucovorin for 1.5 years and 1 year, respectively. A randomized trial is needed to understand whether extended treatment period is beneficial for patients who require adjuvant chemotherapy for stage II and stage III colon cancers.

7. Conclusion

Multiple agents and multi-modality treatment might offer long- term survival in patients with metastatic or recurrent CRC. Oral form of UFUR/ leucovorin may replace 5-FU in the adjuvant setting because of its effectiveness, safety with less side effects and equivalent. OS, avoid complication of central venous catheter, reduced hospitalization and cost, and more freedom for the patients. Patients should be encouraged to take medications for 2 years as adjuvant chemotherapy for CRC following surgical resection.

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