



Cost minimization comparison of oral UFT/leucovorin versus 5-fluorouracil/leucovorin as adjuvant therapy for colorectal cancer in Taiwan

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Aim: Oral uracil–tegafur/leucovorin (UFT/LV) and intravenous 5-fluorouracil (FU)/LV are common adjuvant therapies for Stages II and III colorectal cancer. This study aims to determine the most cost-effective treatment alternative between UFT/LV and 5-FU/LV in Stages II and III colorectal cancer from Taiwan's National Health Insurance perspective. **Patients & methods:** The costs were referenced directly from the National Health Insurance reimbursement price. Chemotherapy regimen considered for the cost analysis calculation was adapted from NSABP-C-06 study, and, a time saving calculation was also included. In addition, we compare the treatment outcome. **Result:** A total cost saving of US\$3620.80–\$3709.16 per patient per treatment was achieved with the UFT/LV treatment. UFT/LV provides the comparable outcome to 5-FU/LV. **Conclusion:** UFT/LV was the more cost-effective treatment as adjuvant chemotherapy.

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Colorectal cancer is the most common malignancy and a major health concern in Taiwan. According to the reports submitted to the Taiwan Cancer Registry, in 2015, it was the most common cancer in men and second most common cancer in women. Colorectal cancer was diagnosed in 15,579 people, accounting for 14.8% of all cancers reported, and 5687 Taiwanese died from this disease [1].

Treatments for colorectal cancer include surgical resection, radiotherapy and chemotherapy. Recently, efforts to improve survival have focused on presymptomatic diagnosis, adjuvant chemotherapy and modification of surgical techniques. Surgical resection is the main approach for colorectal cancer treatment. The curative role of fluorouracil (FU)-based chemotherapy in the adjuvant setting has been shown in a pooled analysis [2]. The goal of adjuvant chemotherapy is to decrease recurrence and increase disease-free survival. Oral uracil–tegafur (known as UFT, or UFUR in Taiwan), containing tegafur and uracil in a 1:4 molar ratio, is an oral antineoplastic agent used in the management of gastrointestinal cancer [3,4]. Oral uracil–tegafur alone or in combination with leucovorin (LV) has been proven to afford better relapse-free survival than that afforded by surgery alone [5,6] and exhibited similar efficacy to that of intravenous 5-FU/LV with a better toxicity profile and increase in convenience in adjuvant [7], metastatic [8,9] and postoperative concurrent chemoradiation settings [10]. Between 2008 and 2012, the 5-year survival rates for Stages I, II, III and IV colorectal cancer were 81.3, 71.3, 59.1 and 11.4%, respectively [11].

While 5-FU/LV is an effective treatment, the cost–effectiveness evaluation, especially that of the economic benefit of an alternative treatment, is being increasingly performed. Several studies have examined the economic impact of alternative oral chemotherapy compared with intravenous chemotherapy. Many studies were based on Stage III colorectal cancer. Studies in Taiwan [12] and Japan [13] showed capecitabine as an alternative to the 5-FU backbone, with a better health outcome and lower cost compared with those associated with 5-FU/LV in the adjuvant treatment of stage III colon cancer. However, there were no comparative studies on UFT/LV and

5-FU/LV in an adjuvant setting. Although, Norum *et al.* [14] had examined the cost–effectiveness of 5-FU and levamisole in an adjuvant setting, this chemotherapy combination was not a popular choice in Taiwan. Since the use of oral UFT/LV or 5-FU/LV in adjuvant treatment for colorectal cancer is a common practice in Taiwan, it is important to understand the economic impact of these alternative regimens by comparing their costs.

The purpose of this study was to compare the costs of oral UFT/LV and 5-FU/LV, which are reimbursed by the National Health Insurance (NHI) of Taiwan as adjuvant treatment for Stages II and III colorectal cancer. Previous pharmacoeconomic studies have shown that oral UFT/LV treatment is more cost- and time-saving compared with 5-FU/LV in a metastatic setting [15–17]; however, these studies do not reflect Taiwan's prevailing conditions. Furthermore, there are no comparative studies between oral UFT/LV and 5-FU/LV in an adjuvant setting. The fact that the healthcare system in Taiwan is a government-run, single-payer system with a universal insurance coverage program covering 99% of the population, it is essential to determine the cost–effectiveness of the two chemotherapy regimens.

Methods

We performed a cost-minimization procedure to compare the cost–effectiveness of oral UFT/LV and intravenous 5-FU/LV, since they were found to have similar efficacy [7–10]. Regimens from NASBP-C-06 [7] were used for the cost calculation, because it was the largest study comparing oral UFT/LV to 5-FU/LV in an adjuvant setting. In brief, the oral UFT/LV regimen comprised five 5-week cycles consisting of 4 weeks of UFT (300 mg/m²/day) and LV (90 mg/day) and a 1-week rest period. The intravenous 5-FU/LV regimen consisted of three 8-week cycles of weekly 5-FU (500 mg/m²) and LV (500 mg/m²) for 6 weeks and a 2-week resting period (Rosewell Park regimen). The costs of chemotherapy drugs were based on the 2012 NHI reference list for drugs, and the costs of medical consultation, drug infusion and hospital admissions were based on the Fee Schedule for Medical Services [18]. All the costs used in the analysis were referenced from the NHI reimbursement price list to reflect Taiwan's condition from the payer's perspective. The direct cost of each treatment was calculated by multiplying the unit cost by medical resource utilization.

In Taiwan, there are two brands of oral uracil–tegafur: UFT (Otsuka Pharmaceutical, Tokyo, Japan) and UFUR (TTY Biopharm, Taipei, Taiwan). NHI covers these two brands and intravenous 5-FU for Stages II and III colorectal cancer adjuvant therapy. It was also suggested in the treatment guidelines to treat high-risk Stages II and III colorectal cancer patients with oral UFT/LV or 5-FU/LV adjuvant therapy. Cost–effectiveness calculations included both UFT and UFUR owing to their different NHI prices of NT\$69 and NT\$73, respectively. Since there are numerous brands of infusion regimens for 5-FU and both infusion and oral LV, the lower and upper price range of each chemotherapy agent is shown in the table, but for the ease of calculation, only the price of the most commonly used agent at the time of analysis for each product is selected. It is assumed that the body surface area is 1.6 for all colorectal patients. All calculations are in US\$ (US\$1.00 = NT\$31.687, exchange rate in 2017) [19]. Moreover, data from a local expert panel survey were considered to provide a true comparison of the cost–effectiveness of the oral and intravenous regimens. In brief, the expert panel consisted of 12 Taiwanese colorectal surgeons and medical oncologists. The survey revealed that approximately 69.6% patients received outpatient department bolus 5-FU regimen and approximately 30.4% received an in-patient department infusion. The cost of hospital stay was also included in treatment cost calculation for patients who required in-patient department infusion.

With respect to time saving, as was shown in the Maroun *et al.* study [12], this study also included calculation based on the number of clinic visits and treatment duration. In brief, patients receiving oral chemotherapy would require a monthly clinical checkup, and five visits in the whole course of treatment. Patients on intravenous chemotherapy would require a weekly clinical checkup, six visits per cycle, and 18 visits in the whole treatment course. Additionally, these patients would need to spend 4 h in the chemotherapy unit (CTU) for premedication and chemotherapy infusion. Moreover, 5-FU/LV patients would require a one-time central venous catheter implantation for approximately 100 min.

One-way sensitivity analyses were performed to test the robustness of the model. The sensitivity analyses varied key assumptions in the model, including the acquisition costs of chemotherapy drugs and medications for AEs, drug administration costs, utilities and discount rates.

Results

Cost saving

The unit costs used in the analysis of UFT/LV and 5-FU/LV therapies are shown in Table 1. Although both the

Table 1. Unit cost of the resources used in the analysis.

Chemotherapy drug cost	US\$	Source
UFT (100 mg)	\$ 2.18	BNHI RLD
UFUR (100 mg)	\$ 2.31	BNHI RLD
LV (15 mg)	\$ 0.77	BNHI RLD
5-FU (50 mg/ml, 20 ml)	\$ 3.63	BNHI RLD
LV inj (10 mg/ml, 5 ml)	\$ 3.44	BNHI RLD
Drug administration		
Physician consultation	\$ 11.05	BNHI FSMS
Premedication	\$ 113.46	BNHI FSMS
Complete blood count	\$ 12.50	BNHI FSMS
Intravenous drug administration (1–4 h)	\$ 46.71	Mackay Memorial Hospital
Central venous catheter surgery	\$ 94.67	BNHI FSMS
Central venous catheter device	\$ 327.27	BNHI FSMS
Hospital admissions (per day)	\$ 37.24	BNHI FSMS
Adverse event management		
5-FU adverse event management	\$ 628.14	Expert panel survey
Oral uracil–tegafur adverse event management	\$ 124.38	Expert panel survey

BNHI FSMS: Bureau of National Health Insurance of Taiwan fee schedule for medical services; BNHI RLD: Bureau of National Health Insurance of Taiwan reference list for drugs; FU: Fluorouracil; LV: Leucovorin.

Table 2. Mean cost per patient by treatment and type of cost.

Item cost	5-FU/LV	UFT/LV	Net savings (UFT/LV – 5-FU/LV)	UFUR/LV	Net savings (UFUR/LV – 5-FU/LV)
Chemotherapy drugs	\$ 1173.61	\$ 2046.52	\$ 872.92	\$ 2134.89	\$ 961.28
Visit for drug administration	\$ 198.82	\$ 55.23	-\$ 143.59	\$ 55.23	-\$ 143.59
Drug administration-related cost	\$ 3574.21	\$ 62.49	-\$ 3511.72	\$ 62.49	-\$ 3511.72
Central venous catheter-related cost	\$ 421.94		-\$ 421.94	\$	-\$ 421.94
Physician consultations for adverse events	\$ 11.05	\$ 11.05		\$ 11.05	
Adverse event management	\$ 628.14	\$ 123.34	-\$ 504.81	\$ 123.34	-\$ 504.81
Total	\$ 6007.76	\$ 2298.60	-\$ 3709.16	\$ 2386.98	-\$ 3620.80
Hospital stay for drug administration (2 nights)	\$ 1340.61		-\$ 1340.61		-\$ 1340.61
Total including hospital stay	\$ 7348.37	\$ 2298.60	-\$ 5049.77	\$ 2386.98	-\$ 4961.41

FU: Fluorouracil; LV: Leucovorin.

oral and intravenous regimens could be completed in an outpatient setting, 5-FU/LV has to be administered in an outpatient CTU, which costs US\$46.71 per administration for infusion of less than 4 h. The 5-FU/LV regimen also requires premedication, which costs US\$113.46 per administration. Table 2 provides the estimated average costs associated with UFT/LV and 5-FU/LV therapies. The drug cost for 5-FU/LV was US\$1173.61, lower than that for both brands of oral UFT/LV (US\$2046.52 for UFT and US\$2134.89 for UFUR). However, after taking chemotherapy administration cost and adverse effect management cost into consideration, oral UFT/LV showed a total cost saving of US\$3620.80–\$3709.16 per patient per treatment (Table 2). The medical cost saving of oral UFT/LV was seen primarily in drug administrations (US\$62.49 for oral UFT/LV vs US\$3574.21 for 5-FU/LV). The cost for a one-time central venous catheter installation was US\$421.94.

Time saving

Patients on oral uracil–tegafur regimen required less clinical visits as opposed to those on 5-FU/LV (Table 3). Patients on 5-FU/LV regimen required a weekly visit, which accounts for 18 clinical visits for the whole course of chemotherapy administration, and patients on oral UFT/LV regimen would only require five clinical visits. Thus, a patient administered with UFT/LV regimen instead of 5-FU/LV regimen would need <13 less clinic visits and

Table 3. Chemotherapy treatment unit time and visit per treatment regimen.

Types of treatment	Visit/cycle per patient	Total treatment visits per patient	Time (min)/CTU visit	Time (h) in CTU/ patient	Visit × 50 patient
Oral uracil–tegafur	1	5	0	0	250
5-FU/LV (Rosewell Park)	6	18	240	72	900

Patients on oral regimen would require five cycles of monthly visits to the clinic, whereas patients on infusion therapy would require three cycles of six weekly visits.
CTU: Chemotherapy treatment unit; FU: Fluorouracil; LV: Leucovorin.

Table 4. Chemotherapy treatment unit and visits saved by oral uracil–tegafur comparing to 5-fluorouracil/leucovorin (per 50 patients of total treatment).

Hours of treatment	Oral uracil–tegafur	5-FU/LV
Number of visits for 50 patients	250	900
Hours for central venous catheter implantation [†]	0	83
Hours in CTU	0	3600
Total hours (CTU plus Port-A implant)	0	3683

[†] Average infusion time is 1 h and 30 min.

CTU: Chemotherapy treatment unit; FU: Fluorouracil; LV: Leucovorin.

save up to 72 h in the CTU. From experience, it is highly likely for patients on a 5-FU/LV regimen to have >18 clinical visits owing to adverse side effects.

Treatment outcome

Our patients also did prove that adjuvant chemotherapy with UFT/LV may replace 5-FU/LV with equivalent disease-free survival, overall survival and well tolerated. It also suggests that there is no benefit of better outcome for patients who had FOLFOX chemotherapy compared with patients who had UFUR and LV (complete data in the supplement).

Discussion

While we found lower costs for 5-FU/LV chemotherapy than oral uracil–tegafur/LV regimen, the lower costs were offset by the higher administration cost of 5-FU/LV, leading to a remarkably lesser total treatment cost for UFT/LV and UFUR/LV regimen. This result was similar to another cost-effective analysis comparing another oral chemotherapy with 5-FU/LV as adjuvant therapy for stage III colon cancer in Taiwan. In that study, the cost of the oral chemotherapy was higher than 5-FU/LV, but the overall cost saving was found to be significant after considering drug administration costs [12]. In our study, UFT/LV and UFUR/LV showed a total cost saving of \$3709.16 and \$3620.80 per patient per treatment, respectively (Table 2). However, the cost for 5-FU/LV was underestimated in our report since the cost and time spent on cleaning central venous catheter and infection handling were not included in this calculation. In addition, Rosewell Park regimen for 5-FU/LV was used for the calculation. This intravenous regimen is a weekly bolus 5-FU/LV, which could be administered within four infusion time so patients could complete the administration in an out-patient CTU. According to a Taiwan local expert panel survey on intravenous 5-FU adjuvant treatment of colorectal cancer, approximately 30.4% of patients would receive an in-patient department infusion of 5-FU regimen for adjuvant treatment. Thus, some patients treated with 5-FU/LV might spend at least a night or longer if physicians chose to have longer 5-FU infusion time regimens. In our net saving calculation, we found that UFT/LV and UFUR/LV regimen for a needed in-patient infusion could save up to a maximum of \$5049.77 and \$4961.41 per patient, respectively.

A cost comparison of UFT/LV to 5-FU/V in metastatic setting was done in Canada [16] based on data from two randomized trials showing a cost saving of CAN\$ 3221 per patient per treatment and 4.5 h saved per patient per month. Maroun *et al.* described that one of the key advantages in oral uracil–tegafur treatment is to increase the efficiency in hospital setting [16]. In their studies, UFT treatment saved 225 h per month in the CTU. Alternating chemotherapy regimens with similar efficacy and requiring less space and time allocation in the CTU would be a great relief for the medical staff [16]. In our study, patient on oral uracil–tegafur/LV regimen required 13 less clinic visits and saved 72 h (Tables 3 & 4).

From the hospitals' perspectives, a total of 3683 h could be saved from treatment of 50 colorectal patients. It is very likely for a hospital to have >50 colorectal patients since it is the most common malignancy in Taiwan. This would be equivalent to 600 h saved per month in CTU. Medical staff could spend less time administering therapy that could otherwise been given orally. Administration by infusion using a central vein catheter involves substantial costs, whereas replacing 5-FU/LV with oral therapy results in savings in health resources for the hospital and the government.

The oral uracil–tegafur regimen also provides patients a better treatment alternative over 5-FU/LV. The advantage of oral regimen out-weighted intravenous regimen is mainly due to its convenience [20] and lesser toxicity [8]. Oral uracil–tegafur regimen may be associated with less inpatient services and less work loss [21]. At least two studies have shown that patients prefer oral chemotherapy over intravenous therapies if efficacy is not compromised [22,23]. In Borner *et al.* study, 84% of the patients preferred the oral uracil–tegafur regimen. The roles of oral UFT/LV in adjuvant [7,10] and metastatic settings have been proven to have similar efficacy as with intravenous 5-FU/LV [8,9]. Reasons for preference of the oral uracil–tegafur regimen include being able to take medication at home, less stomatitis and being able to use a capsule instead of an injection [23]. In addition, some patients may need to stay at hospital for infusion and a longer stay would mean productivity loss, higher economic burden for the family and a higher chance of central vein catheter complications, such as infection, bleeding, pneumothorax and venous thromboembolism.

Several limitations should be noted when interpreting the study results. The price used was based on the NHI price in Taiwan so it may not reflect condition in other counties. In addition, the reimbursement price of chemotherapy was based on values collected in 2013, which may not reflect the price of chemotherapy in 2014 or later. Nonetheless, our study focused on the real condition in Taiwan, where both 5-FU/LV and oral UFT/LV are reimbursed by NHI. Finally, the costs for intravenous drug administration and for oral 5-FU and uracil–tegafur adverse event management were estimated based on one single hospital and an expert panel survey, respectively, and thus may not reflect the real range of these costs. We attempted to address this issue by varying the estimated costs by $\pm 20\%$ to assess the robustness of the study results. Our finding suggested that even with a 20% variation in the costs of intravenous drug administration and adverse event management, the total costs for the UFT/LV regimen remained lower than the 5-FU/LV regimen.

Conclusion

In Taiwan, NHI reimburses the medical cost of oral uracil–tegafur (UFUR and UFT) and 5-FU for Stages II and III colorectal cancer adjuvant chemotherapy. The government's viewpoint is that the oral chemotherapy has an advantage over the intravenous regimen, attributed to the savings in administration and improvements seen during adverse events. The study reflected a total cost saving per patient of US\$3620.80–\$4961.41 (UFUR) and US\$3709.16–\$5094.77 (UFT), along with 72 h less time spent per patient. This would lead to cost- and time-effective utilization of the wards.

Summary points

- This analysis is the first comparative study between oral UFT/leucovorin (LV) and 5-fluorouracil (FU)/LV in an adjuvant setting.
- This analysis determines the most cost-effective treatment alternative between UFT/LV and 5-FU/LV in Stages II and III colorectal cancer from Taiwan's National Health Insurance perspective.
- This result was similar to another cost-effective analysis comparing another oral chemotherapy with 5-FU/LV as adjuvant therapy for Stage III colon cancer in Taiwan.
- In our study, UFT/LV and UFUR/LV showed a total cost saving of US\$3709.16 and \$3620.80 per patient per treatment, respectively.
- In our net saving calculation, we found that UFT/LV and UFUR/LV regimen for a needed inpatient infusion could save up to a maximum of \$5049.77 and \$4961.41 per patient, respectively.
- Our patients also did prove that adjuvant chemotherapy with UFT/LV may replace 5-FU/LV with equivalent disease-free survival, overall survival and well tolerated.
- In our study, patient on oral uracil–tegafur/LV regimen required 13 less clinic visits and saved 72 h.
- Our finding suggested that even with a 20% variation in the costs of intravenous drug administration and adverse event management, the total costs for the UFT/LV regimen remained lower than the 5-FU/LV regimen.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2018-0078

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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