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"Real World" Effectiveness of Different Postoperative Adjuvant Chemotherapy Regimens in Stage III Colon Cancer Patients

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Abstract

Background: The benefit of oxaliplatin as postoperative adjuvant chemotherapy in the real world practice remained further clarified. Clinically, choosing oral 5-FU drug or FOLFOX regimen may depend to drug toxicity and patient's age and comorbidities.

Methods: Patients included in this study was from Chang Gung Memorial Hospital (CGMH) colorectal cancer registry database. Treatment outcomes were compared based on the type of chemotherapy in terms of OS and DFS. Multivariate Cox-regression modelling was used to adjust for the potential confounders.

Results: Between 2007 Jan and 2012 Dec, 688 stage III colon cancer patients were collected including fluorouracil-leucovorin plus oxaliplatin (FOLFOX-6) (283 patients), Capecitabine (259 patients), and Tegafur-uracil (146 patients). Patients receiving FOLFOX-6 were significantly younger (mean age 56.5 yrs *vs* 65,1 yrs and 66,9 yrs), more poor differentiation (15.9% *vs* 8.1% and 8.2%), deeper tumor invasion (T4 lesion 25.1% *vs* 15.8% and 17.1%), more advanced nodal involvement (N2/3 51.9% *vs* 18.1% and 20.5%) and had less comorbidity (50.2% *vs* 61.4% and 65.1%). Rate of completeness of chemotherapies (88.0% *vs* 87.6% and 81.5%) was no significant difference. Treatment outcome, by balancing confounding factors including co-morbidities, multivariate analysis showed that impact on OS in patients receiving FOLFOX-6 regimen was no difference comparing with capecitabine (HR=1.32, p=0.32) while Tegafur-uracil was statistically significant worse than Tegafur (HR=1.69, p=0.03). However, disease free survival (DFS) was no significantly different for FOLFOX-6 (HR 0.97, p=0.88) and Tegafur (HR 1.08, p=0.72) comparing with capecitabine.

Conclusions: In this retrospective study, as post-operative adjuvant setting, we found oral chemotherapy (Capecitabine or UFUR) compared with FOLFOX-6 for stage III colon cancer patients demonstrated similar DFS after balancing bias on imbalanced use of oxaliplatin-based chemotherapy.

Keywords: Chemotherapy; Drugs; Dosage of drug; Colon cancer; Adjuvant; Treatment

Backgrounds

Over the past two decades, the combination of 5-FU and leucovorin (LV) was suggested in the stage III or high risk stage II colon cancer as the adjuvant setting despite no standard schedule of 5-FU/LV has been established [1,2]. Recently, studies comparing oral form of 5-FU drug with infusion 5-FU showed similar effectiveness [3,4]. The X-ACT trial compared capecitabine with bolus 5-FU/LV alone and showed not inferior efficacy for oral capecitabine [3]. Another oral 5-FU drug, Tegafur-uracil (UFUR) was widely used in Asia countries. The Kato study showed similar efficacy of UFUR the adjuvant setting too [4]. These two oral forms of 5-FU drugs have been continuously used in Taiwan since their introductions in 1999 and 2001 respectively. Later, based on MOSAIC trial [5], Xeloxa trial [6] and NSABP C-07 [7] randomized clinical trials (RCTs), the addition of oxaliplatin to adjuvant 5- fluorouracil (5-FU) improve both progression free survival (PFS) and overall survival (OS) of patients with stage III colon cancer [5-7]. After these papers published, oxaliplatin and fluoropyrimidine-based therapy (FOLFOX), despite some modifications, rapidly became the predominant adjuvant treatment for stage III colon cancer in the world. However, clinically there are several factors limiting clinician to adhere to FOLFOX regimen such as consideration of neurotoxicity of oxaliplatin and patients' comorbidities. In addition to patient age affecting choice of adjuvant therapy, there is also inconsistency regarding oxaliplatin benefit in patients age older than 70 [8,9].

Furthermore, the impact of medical comorbidity remained to be further clarified in previous studies [9]. Some also argued against participants in RCTs are usually younger, and healthier than the general cancer population. In clinical practice, the patients treated were more complex because they may take other drugs affecting efficacy of chemotherapy regimens. Moreover, previous trials did not clearly indicate that if the heterogeneous group of stage III colon cancer patients, such as status of molecular profile with same benefit from FOLFOX regimen [10,11].

Thus the benefit of FOLFOX as adjuvant setting in the real world practice remained further investigated. Moreover, little is known about follow up status of guideline recommended for postoperative adjuvant chemotherapy of colon cancer patients in clinical practice. Little is

known to what extent patient's co-morbidities would affect the outcomes of post-operative adjuvant chemotherapy. We thus retrospectively reviewed outcomes of adjuvant chemotherapy in our stage III colon cancer patients related to varied clinical variables and types of adjuvant chemotherapy.

Patients and Methods

The data source for this study was from Chang Gung Memorial Hospital (CGMH) colorectal cancer registry database. This database was first established in 1985 and a revised data record form was implemented in 1995 (9). Data collected included six major parts comprising detailed family history, demographic variables, preoperative evaluation, operation records, multidisciplinary treatment including chemotherapy and postoperative follow-ups. Through patient interviews and from clinical and pathological records, all data are recorded by surgical nursing specialists on a standardized form and confirmed by one of the authors (JF You or HY Hung) before being translated into a numeric code and keyed in the computer for record and following up by nurse specialists.

The chemotherapy record included chemotherapy aim, chemotherapy strategy, chemotherapy mode, chemotherapy interval, chemotherapy drugs, dosage of drug, completeness of chemotherapy, cause of termination, duration of chemotherapy, dose reduction and toxicity and concurrent therapy. In addition to chemotherapy details as describe above, data collected from the databases for each patient included demographic data; gender, age, co-morbidity and date of recurrence and date of death. The cut-off date for data collection on patient treatments and outcomes for each cohort was 31 Dec 2014.

In this study, stage III colon cancer patients post curative intent surgery then received adjuvant chemotherapy were collected. Treatment outcomes were retrospectively compared among three cohorts, which were constructed based on the type of chemotherapy, that is, FOLFOX, Capecitabine and Tegafur-uracil, in terms of overall survival (OS) and disease free survival (DFS). Since different timeline of reimbursement of chemotherapy drugs in Taiwan, Oxaliplatin was initially approved to the reimbursement of Taiwan National Health Insurance in April 2009 for an indication of post-operative adjuvant treatment of stage III colon cancer. The introduction of oxaliplatin since 2007 and then FOLFOX regimen as stage III colorectal cancer patients as standard treatment was established in our hospital. We therefore chose data from 2007 to 2012 because during these periods, all these three drugs used are public funding without insurance preference.

Statistical analyses

Statistical analysis was performed to compare outcomes among three cohorts, in order to evaluate a possible interaction of benefit from oral form 5FU chemotherapy and the oxalinplatin chemotherapy. OS and DFS curves were generated using the Kaplan-Meier method. Multivariate Cox-regression modeling was used to adjust for the following potential confounders: age, gender, presence of comorbidity, operation findings such as perforation, obstruction, combined other organ resection and tumor characteristics such as histology, grading, tumor invasion depth, nodal involvement status. Statistical significance of comparisons of the three cohorts was determined using the t-test and the $\chi 2$-test. All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (Chicago, IL, USA).

Results

The study included 688 patients. Baseline patient demographic characteristics were shown in Table 1. The administered regimens were: Capecitabine (260 patients), FOLFOX (282 patients) and UFUR (146 patients). Comparing with oral chemotherapy either Capecitabine or UFUR, patients receiving oxaliplatin based chemotherapy (FOLFOX) were younger mean age was 56 Y/O (*vs* 65 y/O and 66 y/O for capecitabine and UFUR respectively). Old age patients (age older than 70 y/o) for FOLFOX regimen were 11.0% compared with UFUR and Capecitabine (41.5% and 55.5%, p<0.0001). Patients underwent FOLFOX were associated with more mucinous adenocarcinoma (8.5% Haineng Xu 3.5% and 5.5%, p=0.0444), more poor differentiation (16.3% *vs* 7.7% and 8.2%, p=0.0028), deeper tumor invasion T4 lesion(25.2% *vs* 15.4% and 17.1%, p=0.0111), more advanced nodal involvement N2/3 (51.8% *vs* 18.5% and 20.6%, p<0.0001) and less comorbidity (50.2% *vs* 61.4% and 65.1%, p=0.0035) than patients with oral chemotherapies either Capecitabine or UFUR.

	Chemotherapeutic regimen			**X2 test, p-value**
Age, mean(SD)	**Capecitabine n=260**	**UFUR n=146**	**FOLFOX n=282**	
<50 y/o	25(9.6)	14(9.6)	75(26.6)	<0.0001
50-69 y/o	127(48.9)	51(34.9)	176(62.4)	
≥ 70 y/o	108(41.5)	81(55.5)	31(11.0)	
Gender				**0.7804**
Female	110(42.3)	67(45.9)	122(43.3)	
Male	150(57.7)	79(54.1)	160(556.7)	
Operation type				**0.1005**
regular	254(97.7)	139(95.2)	278(98.6)	
emergency	6(2.3)	7(4.8)	4(1.4)	
OP complication				**0.1512**
without	248(95.4)	136(93.2)	274(97.2)	
with	12(4.6)	10(6.8)	8(2.8)	
Combined operation				**0.5488**
No	206(79.2)	120(82.2)	219(77.7)	
Yes	54(20.8)	26(17.8)	63(22.3)	
Histology				**0.0444**
adenocarcinoma	251(96.5)	138(94.5)	258(91.5)	
Mucinous/signet	9(3.5)	8(5.5)	24(8.5)	
Tumor grade				**0.0028**
Well/Mod	240(92.3)	134(91.8)	236(86.7)	
poor	20(7.7)	12(8.2)	46(16.3)	
TMN_T stage				**0.0111**
1, 2, 3	220(84.6)	121(82.9)	211(74.8)	

4	40(15.4)	25(17.1)	71(25.2)	
TMN_N stage				**<0.0001**
1	212(81.5)	116(79.5)	136(48.2)	
2, 3	48(18.5)	30(20.6)	146(51.8)	
Co-morbidity				**0.0035**
No	100(38.6)	51(34.9)	141(49.8)	
Yes	159(61.4)	95(65.1)	142(50.2)	
No. of co-morbidity mean(SD)	**1.0 (1.0)**	**1.2 (1.2)**	**0.8 (1.0)**	**0.0015**

Table 1: Baseline characteristics of stage III colon cancer patients receiving different adjuvant chemotherapy regimen.

Five year disease-free survival probability of patients in this study receiving FOLFOX was 62.3% which was comparable to MOSAIC trial results [5]. Capecitabine and UFUR were 74.8% and 71.7% respectively. Five year overall survival for patients with FOLFOX was 77.7%; 79.9% for Capecitabine while 69% for UFUR.

Cox model D, covariates	P value	Adjusted HR (95% C.I.)
Tegafur *vs*. Capecitabine	0.03	1.69(1.05-2.70)
FOLFOX *vs*. Capecitabine	0.3219	1.32(0.76-2.27)
Age, per 10 increases	<.0001	1.59(1.30-1.94)
Gender, male *vs*. female	0.7919	1.06(0.70-1.60)
Operation, emergency *vs*. regular	0.1812	0.50(0.18-1.38)
OP findings, yes *vs*. no	0.3036	1.30(0.79-2.16)
Combined resection yes *vs*. no	0.647	1.12(0.7-1.78)
HT mucinous/signet *vs*. adenocarcinoma	0.5972	0.78(0.31-1.95)
HG poor *vs*. well/moderate	0.071	1.81(0.95-3.46)
TMN_T, T4 *vs*. T1-T3	<.0001	3.02(1.98-4.62)
TMN_N, N2 and N3 *vs*. N1	0.0001	2.27(1.50-3.45)
No. of comorbidity	0.1669	1.14(0.95-1.36)

Table 2: Adjusted Hazard Ratio of clinical features related to overall survival.

Comparing treatment outcome among three chemotherapy regimen cohorts, by univariate analysis, demonstrated marginal significant difference in OS (p=0.654) (Figure 1) but no significant different PFS (Figure 2) between different chemotherapy cohorts. However, by balancing confounding factors, multivariate analysis showed that patients receiving Capecitabine was statistically significantly showing better OS than patients receiving UFUR (HR=0.57, 95% CI 0.35–0.90, p=0. 0171) while no difference comparing patients with FOLFOX regimen (HR=0.74, 95% CI 0.43–1.28, p=0.2810) (Table 2 and Figure 3). Furthermore, for N 1 subgroup analysis, multivariate analysis still revealed better OS for Capecitabine compared to UFUR regimens (HR=0.55, 95% CI 0.30–1.01, p=0.0544), while for N2/3 subgroups, no significant difference found between FOLFOX, Capecitabine and UFUR. However, there was no significant difference of DFS between different chemotherapy regimens (Table 3 and Figure 4).

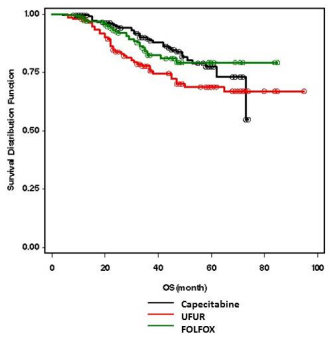

Figure 1: Comparisons of overall survival between different chemotherapy regimens.

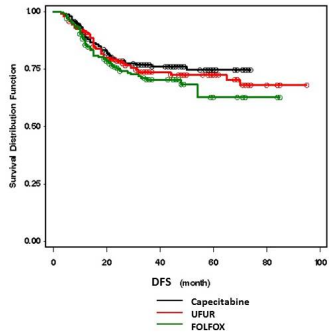

Figure 2: Comparisons of disease free survival between different chemotherapy regimens.

There was no significant difference was found in terms of completeness of chemotherapy course, (Table 4) neither do toxicities (Table 4). The planned dose for each regimen was equal to the dosing recommendations of the guideline. We found that average 80.6% and 81.2% of the recommended dose was given in Capecitabine and UFUR. The dosages reduction rate and duration for administration between different regimens were not significant different (Table 4). However, non-compliance of patient underwent UFUR was 8.2% that was higher than FOLFOX (2.5%) and capecitabine (5.8%) groups.

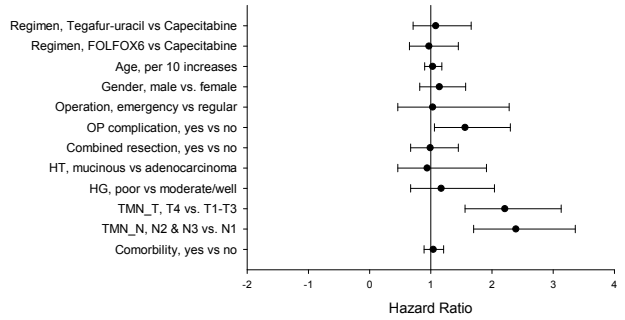

Figure 3: Adjusted Hazard Ratio of clinical features related to overall survival.

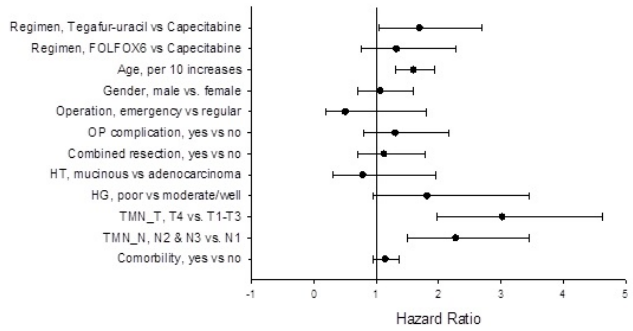

Figure 4: Adjusted Hazard Ratio of clinical features related to disease free survival.

Tegafur *vs*. Capecitabine	0.7157	1.08(0.71-1.66)
FOLFOX *vs*.Capecitabine	0.8784	0.97(0.69-1.45)
Age, per 10 increases	0.5733	1.04(0.91-1.18)
Gender, male *vs*. female	0.4315	1.14(0.82-1.57)
Operation, emergency *vs*. regular	0.9652	1.02(0.46-2.25)
OP findings, yes *vs*. no	0.0251	1.55(1.06-2.28)
Combined resection yes *vs*. no	0.9392	0.99(0.67-1.45)
HT mucinous/signet *vs*. adenocarcinoma	0.8926	0.95(0.47-1.93)
HG poor *vs*. well/moderate	0.5869	1.17(0.67-2.03)
TMN_T, T4 *vs*. T1-T3	<.0001	2.21(1.56-3.13)
TMN_N, N2 and N3 *vs*. N1	<.0001	2.40(1.71-3.37)
No of co-morbidity yes *vs* no	0.6425	1.04(0.89-1.21)

Table 3: Adjusted Hazard Ratio of clinical features related to disease free survival.

Chemotherapy Regimen				
Completeness of course	Capecitabine	Tegafur-urecil	FOLFOX	p value
	pt. No.(%)	pt. No. (%)	pt. No. (%)	
Yes	227 (87.6%)	119 (81.5%)	249 (88.0%)	0.1396
No	32 (12.4%)	27 (18.5%)	34 (12.0%)	
Disease progression	10 (3.9%)	10 (6.8%)	11 (3.9%)	0.0603
Unacceptable toxicities	6 (2.3%)	3 (2.1%)	15 (5.3%)	
Patient noncompliance	15 (5.8%)	12 (8.2%)	7 (2.5%)	
Patient death	1 (0.4%)	2 (1.4%)	1 (0.4%)	
Dose Reduction	3 (9.4)	3 (8.8)	0 (0.0)	0.2682
No. of months prescribed	5.6 (1.95)	6.0 (2.28)	5.9 (1.55)	0.1404
(Mean ± SD)				

Table 4: Chemotherapy courses and toxicities.

Discussions

In this retrospective study, based on clinical practice data, we found that FOLFOX-6 were used among patients with significantly younger, more poor differentiation, deeper tumor invasion, more advanced nodal involvement (N2/3) and had less comorbidity [12]. However, by using multivariate analysis and Cox regression analysis to balance bias on patient outcome related to the imbalanced use of oxaliplatin-based chemotherapy, we found that no significant longer PFS in the FOLFOX cohort comparing with capecitabine and tegafur-uracil cohorts. Overall survival of the capecitabine as post-operative adjuvant chemotherapy for stage III colon cancer patients was also not significantly different from FOLFOX, while significantly better than chemotherapy with UFUR.

Patients with completely resected stage III colon cancer should be offered adjuvant chemotherapy. However, cost effectiveness and quality of life of adjuvant chemotherapy are major concerns in the "real world" [13,14]. Uncertainty remains regarding the optimal treatment of elderly patients and patients with comorbidities [8-10]. Although FOLFOX as adjuvant treatment for stage III colon cancer are generally well followed in daily practice because of additional 6-8% disease free survival benefit for patients comparing with 5-FU regimen alone, real-world efficacy of oxaliplatin in stage III colon cancer remained unclear. Furthermore, oxaliplatin causes significant neurotoxicity and continued beyond 2 years for some patients. High rate of early discontinuation of FOLFOX up to 30% was observed in one recent study [10]. In our study, we did not found grade 3/4 toxicity significant higher in FOLFOX group (5.3%) than Capecitabine (2.3%) and UFUR (2.1%). However, the completeness rate of FOLFOX (81.6%) was lower than Capecitabine (88.6%) and comparable to UFUR (77.1%). The grade 3/4 toxicity in this study was relative lower than reported before maybe due to medium dosage of oxaliplatin (85 mg/m^2) used in our study. For patients received FOLFOLX regimen, another surgery for Port implantation is needed, and some of them need in hospital stay 2 days for continuous 5-Fu infusion. Obviously, oral chemotherapy either capecitabine or tegafur-uracil regimen is superior to FOLFOX in terms of quality of life [13,14].

Moreover stage III colon cancer is a heterogeneous disease, at least, it could be further subgroup into IIIa, IIIb, and IIIc. It is too simply to given all stage III patients same regimen with FOLFOX as postoperative adjuvant treatment rather than to selectively prescribe FOLFOX for some stage III patients based on molecular profile [10,11]. Recently, biomarker prediction for the preferred adjuvant systemic chemotherapy option for patients with completely resected stage III colon cancer have been rapidly developed [10,12] to achieve toward the optimal adjuvant chemotherapy. For examples, defective mismatch repair status as a prognostic biomarker of disease-free survival in stage III colon cancer patients treated with adjuvant FOLFOX chemotherapy [15].

Capecitabine is not inferior to infusion is supported by several randomized control trials [3,7,16]. Besides, reduced dosage in the elderly patients with continuous using and best maintenance therapy (CAIRO3 and AVEX studies) were recommended. Treatment should thus depend on factors such as patient suitability and preference, and patients and clinicians must work together to determine the optimal course of treatment. Our data derived from 'real-life' practice, suggest that the use of capecitabine might have had a significant contribution to these outcomes, although more aggressive use of FOLFOX regimen was adopted. For this reason, our data support oral chemo fluoropyrimidine monotherapy as an appropriate treatment option. Fluoropyrimidine monotherapy with tegafur-uracil or capecitabine is an appropriate adjuvant treatment option for patients age ≥ 70 years. However, further study is needed to identify which subsets of older patients derive potential benefit from oxaliplatin-based chemotherapy.

Our cancer registry database provided significant sample sizes assisting in reflecting the actual contribution of chemotherapy. Notwithstanding their limitations, this database studies are still of major importance in examining the impact of treatment in the context of real-world care settings.

Conclusions

In this retrospective study, we found that as post-operative adjuvant setting, FOLFOX-6 were used among patients with significantly younger, more poor differentiation, deeper tumor invasion, more advanced nodal involvement (N2/3) and had less comorbidity. However, oral chemotherapy (Capecitabine or UFUR) compared with FOLFOX-6 for stage III colon cancer patients demonstrated similar DFS after balancing bias on imbalanced use of oxaliplatin-based chemotherapy.

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