The New Ropanasuri Journal of Surgery

Volume 1 | Number 1 Article 4

10-20-2016

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Recommended Citation

Kusnadi, Dana S.; Putranto, Agi S.; Saunar, Rofi Y.; Kekalih, Aria; and Moenadjat, Yefta (2016) "Compliance of Patients with Locally Advanced Colorectal Cancer to Chemotherapy Using FOLFOX compared to XELOX Regimen," *The New Ropanasuri Journal of Surgery*: Vol. 1 : No. 1 , Article 4.
DOI: 10.7454/nrjs.v1i1.4
Available at: https://scholarhub.ui.ac.id/nrjs/vol1/iss1/4

New Ropanasuri Journal of Surgery 2016 Volume 1 No.1:11–15.

The New Ropanasuri Journal of Surgery

OPEN ACCESS
Published by Department of Surgery
Faculty of Medicine, Universitas Indonesia

Compliance of Patients with Locally Advanced Colorectal Cancer to Chemotherapy Using FOLFOX compared to XELOX Regimen

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Email: agi_digestive@gmail.com Received: 20/Mar/2016 Accepted: 28/Jul/2016 Published: 20/Oct/2016
http://www.nrjs.ui.ac.id DOI: 10.7454/nrjs.v1i1.4

Abstract

Introduction. Adjuvant chemotherapy become the treatment of choice in advance colorectal cancer to prevent recurrence. Studies showed that FOLFOX and XELOX regimen has been proven to increase overall survival rate and disease free survival. This study is aimed to compare XELOX response to FOLFOX regimen in our center, which is characterized by advanced stage neoplasm in the first presentation with low compliance. It also aimed to find out affecting factors of such response.

Method. We run a retrospective study enrolled of 133 subjects with colorectal carcinoma of stage III and high–risk stage II who received adjuvant chemotherapy and treated in dr. Cipto Mangunkusumo– and Fatmawati General Hospital. Consecutive sampling was instituted, CEA level and one year mortality rate was recorded as variables of the efficacy, which was then associated with subjects' compliance. Statistical analysis was done using Chi square or Fisher test, and a multivariate logistic regression. Significance was found as the difference met <0.05 with confidence interval of 95%.

Results. We found there is no significant difference between the two regimens with efficacy (p = 0.61). There is significant correlation between the regimen (p = 0.001 and 0.000); with compliance is found much higher in FOLFOX (86% compared to 45%). We also found statistically significant of influencing factors the efficacy, i.e. Karnofsky score >90 (OR = 5.8; p = 0.004), body mass index both of normal and more (OR = 4.7; p = 0.006), and with histopathologic grading of moderate differentiated (OR = 6.3; p = 0.003).

Conclusion. FOLFOX and XELOX regimen has been shown to have a same efficacy in response in our center. However, compliance showed a strong correlation to efficacy and FOLFOX regimen showed much higher rather than XELOX. Karnofsky score and body mass index should be subjects of consideration to increase the response of such adjuvant chemotherapy.

Keywords: *colorertal carsinoma, compliance of adjuvant chemotherapy, Karnofsky score, body mass index.*

Introduction

Colorectal cancer place a second most cancer found in the world and place the third rank in cause of death.[1] In Indonesia this malignancy found to be the third place of the most found cancer, with the incidence of 2.8/100.000 of population and mortality of 9.5%.[2]

Following a surgical curative treatment of a locally advanced colorectal cancer, an adjuvant chemotherapy is required to eliminate possible micro metastasis to prevent the recurency.[3] The regimen of FOLFOX which is consist of 5–Fluorouracil (5–FU), leucovorine, and oxaliplatine, has been proven to be a standard adjuvant therapy in these recent years. The reason is that regimen has been proven to be significantly decreased the risk of recurrence despite increase of survival rate. Later, oral fluoropyrimidine has been developed, i.e. capecitabine, which is a kind of oral chemotherapy that produced fluorouracil in tumor stroma through a three step of enzymatic cascade.

Studies in China and Hongkong showed that the oncologist preferred to use the XELOX (capecitabine and oxaliplatin) regimen rather than FOLFOX (5–FU, LV, and oxaliplatin) as the efficacy of XELOX is not inferior compared to FOLFOX.[4] In addition, XELOX regimen needs no central vein access for its administration.[6] Similar results is shown in Europe and USA.[5,7–10]

Based on the similarity of efficacy in both of regimen has been shown in well–developed countries, the regimen of XELOX is proposed as the alternative of adjuvant chemotherapy.[5,7–10]

Somehow, colorectal patients in our center showed a different characteristic to those in well–developed countries. Mostly, they were diagnosed as a locally advanced carcinoma in the first presentation. Another characteristic in our population is those with low social economic background of non–high degree educated with low compliance. Such a condition bear the idea to find out whether the efficacy of the two regimen is quite like those in well–developed countries. Influencing factors to such efficacy in our population were also the subjects to a study. We hypothesized that the regimen of XELOX shows efficacy higher than FOLFOX in term of response and its compliance.

Carcinoembryonic antigen (CEA) serum, which is an established tumor marker of colorectal cancer is to be used as the parameter to evaluate such efficacy. There were studies showed that CEA level correlated significantly to clinical response and decreased of CEA following chemo–radiation refers to independent prognostic factor to disease free survival following tumor resection. Another study found that CEA is a biomarker in predicting the response to chemotherapy using regimen of 5–FU.[11–12]

Method

We run a cohort retrospective study started in January to December 2014. Enrolling locally advanced colorectal carcinoma who treated with adjuvant chemotherapy in our Department of surgery dr. Cipto Mangunkusumo Gneeral Hospital and Fatmawati General Hospital Jakarta using the regimen of XELOX or FOLFOX. Those with other kind of malignancy, incomplete chemotherapy, treated with different previous chemotherapy regimen, cigarette smoker, and those with diseases affecting CEA level were excluded.

We enrolled of 133 patients with consecutive sampling method. The difference between post–operative and post–chemotherapy CEA level as well as one year mortality rate as variables of the efficacy, and compliance were subjects of statistical analysis. Age, gender, and primary tumor site, body mass index and subjective global assessment, and kind of surgical procedure, time of commencing of the chemotherapy, Karnofsky score, histopathology grading, and TNM clinical staging were other independent variables of such a study.

Statistical analysis with Chi square or Fisher test, and a multivariate logistic regression was carried out using SPSS ver.20 for Windows. Significance was found if $p < 0.05$ with confidence interval of 95%. Ethical committee of Faculty of Medicine Universitas Indonesia approved this study (No 903/UN2.F1/ETIK/2015).\

Results

Out of enrolled 133 subjects, there were 16 of dropped out as we found incompleteness of chemotherapy. There were 52.6% subjects aged less than 50 years old and 56.4% were male. We found of 81.2% subjects with Karnofsky score >90, and 57.1% with SGA A, and 67.1% with normal BMI. There were 57.1% subjects had tumor located in rectum, 21.1% in descending colon, and 14.3% in ascending colon. There were 72.1% subjects of stage III with well differentiation type of 48.1% who diagnosed at the first presentation. Low anterior resection was the most kind of surgery carried out of 33.1% subjects, followed by abdominoperineal resection of 18.8%, anterior resection and right hemicolectomy (each of 17.3%).

We found out of 60% subjects commenced the chemotherapy more than eight weeks following surgery, and of 57.1% subject treated with XELOX– compared to 42.9% subjects with FOLFOX regimen. Out of these subjects, 35.3% did not complied the schedule, majority due to pharmacy availability. Nausea found in of 49.9% subjects as the adverse effect, followed by hematological problems (13.8%) and diarrhea (9.9%) while as hand and foot syndrome was found in 6.6% subjects.

In this study we found that XELOX regimen showed the efficacy same as FOLFOX (74.2% vs 78.2%), with the majority indicated complete response (see table 1**).**

Table 1. Efficacy of XELOX and FOLFOX regimen.

Efficacy	Regimen		Odds Ratio (95% CI)	p value
	XELOX	FOLFOX		
Effective	46 (74.2%)	43 (78.2%)	0.802 (0.341–1.89)	0.614
Not Effective	16 (25.8%)	12 (21.8%)		
Total	62 (100%)	55 (100%)		

Table 2. Correlation between chemotherapy regimen and one year mortality rate

Mortality	Regimen		Odds Ratio (95%CI)	p value
	XELOX	FOLFOX		
Survived	53 (45.3%)	45 (38.5%)	1.31 (0.49–3.5)	0.592
Not survived	9 (7.7%)	10 (8.5%)		
Total	62 (53%)	55 (47%)		

Table 3. Correlation between regimen and compliance.

Regimen	Compliance		p	Odds ratio (CI 95%)
	Comply	Not comply		
FOLFOX	49 (86%)	8 (14%)	0.000	7.566 (3.159–18.123)
XELOX	34 (44.7%)	42 (55.3%)		
Total	83 (62.4%)	50 (37.6%)		

Table 4. Correlation between compliance and efficacy.

Regimen	Compliance	Efficacy		Odds ratio (95% CI)	p
		Effective	Not effective		
XELOX	Comply	30 (48.4%)	3 (4.8%)	8.13 (2.02–32.76)	0.001
	Not comply	16 (25.8%)	13 (21%)		
	Total	46 (74.2%)	16 (25.8%)		
FOLFOX	Comply	40 (72.7%)	3 (5.5%)	40 (6.91–231.59)	0.000
	Not comply	3 (5.5%)	9 (16.4%)		
	Total	43 (78.2%)	12 (21.8%)		

Table 5. Correlation between compliance and one year mortality rate.

Regimen	Compliance	One year mortality rate		p	Odds ratio (95% CI)
		Living	Death		
XELOX	Comply	30 (88.2%)	4 (11.8%)	0.374	1.63 (0.39–6.76)
	Not comply	23 (82.1%)	5 (17.9%)		
	Total	53 (85.5%)	9 (14.5%)		
FOLFOX	Comply	39 (81.2%)	9 (18.8%)	0.625	0.72 (0.07–6.77)
	Not comply	6 (85.7%)	1 (14.3%)		
	Total	45 (81.8%)	10 (18.2%)		

Statistical analysis using Chi square test showed no significant correlation between both of regimen (XELOX and FOLFOX) and response to chemotherapy (p = 0.614). The same result was found in multivariate analysis using regression logistic test (p multivariate = 0.969; Adjusted OR = 1.020 (0.374–2.786). We also found there was no statistically difference between the two regimens (14% and 18%) in regarding one–year mortality rate (p = 0.592) as seen in table 2.

The compliance in subjects who were treated with FOLFOX regimen showed much higher than XELOX. The number of subjects complied in FOLFOX almost two times as XELOX did. Statistically, the compliance to regimen showed significant correlation (p = 0.000) with Odds ratio of 7.566 (3.159–18.123) as seen in table 3 and 4. Both two regimens did show the effective response in those who comply the regimen. Using Chi square test, we found p 0.001 in XELOX and 0.000 in FOLFOX. This p values showed significant correlation between compliance and efficacy. Those with compliance orderly to treatment showed a tendency to escalate the efficacy with Odds ratio 8.13 (2.032–32.76) and 40 (7–231).

However, we found there was no significant correlation between compliance with one–year mortality rate with p 0.374 (XELOX) and 0.625 (FOLFOX) as seen in table 5.

The factors found to have significant correlation to efficacy were, Karnofsky score, body mass index, subjective global assessment, compliance, and tumor histopathology grading, with p value of 0.004 (adjusted OR 5.810, CI 95% 1,770–19,069), 0.006 (adjusted OR 4.731 CI 95% 1.569–14.257), and 0.003 6.330 (adjusted OR, CI 95% 1.906–21.022) respectively. A higher Karnofsky score tends to escalate the efficacy of chemotherapy, which valued is OR 6.551 (2.29–18.72). Consider the nutritional status, it was clear that those subject with normal body mass index and more despite SGA A tends to provide a better efficacy with OR 4.24 and 2.74. In this study ,we found a factor that unable to be modified, i.e. tumor histopathology grading. Tumor grade of well– and moderate differentiated tends to increase efficacy with value of OR 2.77 (1.03–7.43).

Discussion

The efficacy of two regimens has been proven in well developed countries,[5,7–10] as Twelves and colleagues did on X–ACT trial that conclude the two regimen showed equality in efficacy. Thus, XELOX could be used as the alternative for adjuvant chemotherapy.[20] However, our colorectal cancer population have its characteristic which is different to those in well developed countries; with the majority belongs to non–high degree educated background. This inspired us to find out whether efficacy of the two regimen provides also a same result.

Several subject characteristics showed similarity to previous studies. The subjects aged below 70 years old[8,20–21] (95%), predominated by males[21] (56,4%), primary tumor site located in rectum[22] (57%), and histopathology findings showed well– and moderated differentiated adenocarcinoma[23] (80%). No wonder we found most of this population (71,7%) diagnosed as stage III (advanced), showing the difference to those in well developed countries which is stage II.[24,25] This might reflect that cancer screening particularly colorectal malignancy in our population is quite minimal. Another difference showed in our characteristic is laid in the regimen commencing. The regimen is just commenced eight (median, 14) weeks following surgery. Meanwhile, in previous studies conducted (Bos and colleagues,[26] Nachiappa and colleagues[27]) it was concluded that any delay after eight weeks' period in commencing the regimen is followed by significant decrease of overall survival rate.

We used post–operative CEA level compared to post–chemotherapy as the tool to evaluate efficacy, which is categorized as complete response, partial response, stable disease, and progressive disease as Wang and colleagues did.[11,12,25] The reason why we choose CEA as the predictor in efficacy is there were study run and showed the superiority of CEA as the parameter to monitor tumor response to chemotherapy; another study showed suitability of radiologic findings with evaluated CEA level, and consider as one of feasibility. It is realized that there are confounding factors to this CEA level, i.e. cigarette smoker, tumor metastasis and other diseases such as inflammatory bowel disease, pancreatitis, and liver disease.[11,12,25] For this reason, we excluded the subjects with those characteristics.

Furthers, the study is then focused to find out correlation between efficacy of chemotherapy response with mortality rate. In term of the feasibility, we decided to find this rate in relatively short period of one year. We were not focused to overall survival rate and disease free survival rate due to limitation, i.e. data insufficiency. There were no orderly follow up of these subjects; both of short– and long term. Statistically, there were no significant different between the two (p = 0.614). Both of regimen showed efficacy in total number of subjects; 76% with complete and partial response. In perspective of mortality, we found there was no significant correlation between the two group (p = 0.592). This was found like study of X–ACT trial (Twelves and colleagues) that conclude oral capecitabine is an effective alternative compared to 5–FU/FA.[5,7–10,20]

A later study of Twelves et.al (2005) concluded that the administration of capecitabine showed a same efficacy as 5–FU/FA does in term of increase the disease free survival and overall survival of the subjects with colorectal cancer.[5,7–10,20] In this case, should we looked at the mortality rate in one year period as the adjuvant chemotherapy commenced, we found that the mortality rate between the subjects treated with FOLFOX compared to XELOX is not significant (19% compared to 15%). But if we compare to previous studies ever runs, we will find it slightly lower. Wolmark and his co–workers found that one–year survival rate of colorectal cancer subjects is over 90%.[28] Thus, the reason of why in our study we found

lower, is that the subjects' compliance to a treatment might be responsible and refers to a matter of further discussion.

In term of compliance, our study showed a strong correlation to the efficacy, both of XELOX ($p = 0.001$) and FOLFOX ($p = 0.000$), with OR of XELOX 8.13 and OR of FOLFOX 40. This finding showed how important the compliance is in success of the treatment of adjuvant chemotherapy. However, we found more than 35% of subjects treated unordered. Those who treated using FOLFOX regimen found to be higher ordered rather than XELOX did. Complied subjects of FOLFOX group is found doubled than XELOX. This could be explained that the administration of FOLFOX is carried out in ward, in other word, under supervision of a medical personnel. In the other side, the policy and the regulation of pharmacy in drugs providing (capecitabine) often leads to delayed of availability with consequent low of compliance. It was seen in this study that the compliance of XELOX is lower than FOLFOX, although there is no inward requirement as well as oral administration; which is a kind of simplicity of this regimen.

Somehow, through a study we found subjects treated with FOLFOX regimen showed a higher compliance than XELOX, with consequent efficacy of FOLFOX found is higher than XELOX (72.7% compared to 48.4%). Then, it is reasonable for us to recommend FOLFOX rather than XELOX, even though the ward availability should be fulfilled.

To accomplish the study, we also tried to find out several factors influencing the mortality rate, in one–year period. Through a study, again, we found that indeed the efficacy is influenced by other factors. These factors are subjects' performance reflected by Karnofsky score, nutritional status which is reflected by body mass index (BMI) and subjective global assessment (SGA), and histopathology grading with p value of 0.004, 0.006, 0.029, and 0.003 respectively. Using logistic regression test, we found that Karnofsky score is valuable in describing subject's performance to have adjuvant chemotherapy to be applied effectively. This variable showed OR of 5.81. The subjects' nutritional status (BMI and SGA) found to be factors influencing the efficacy was also showed as valuable variables. The value of BMI of normal and more showed a valuable factor increasing the efficacy with OR of 4.73.

Finally, the histopathology grading. It was hypothesized that a better histopathology grading lead to a more effective treatment. It valued with OR of 6.33. It was found like findings of Jessup and his co–workers in United States.[32] Hence, through a study we conclude that all tumors with any histopathology grading influencing the survival rate when the subject treated with adjuvant chemotherapy.

Those are factors non–significantly related to the efficacy, i.e. age of the subject, gender, primary tumor sites, clinical stage of TNM–system, and the prime time to commence the regimen. Thus, we believe that application of adjuvant chemotherapy is reliable to any age,[29] any gender,[29] any primary sites, and both of stage II and III. Perhaps we can adore that a study is a little bit different to those published[26,27] is that we could not find the different effect of treatment commenced at the eight weeks of period post–operative with those to earlier.

Meanwhile, previous studies evaluated the efficacy in term of over survival rate and disease free survival rate; somehow, we found insufficient data for a long term follow up and thus we decided to set the point of one–year survival rate. This insufficiency is somehow due to lack of follow up, and we found also the information that this might be due to minimal subjects' awareness. Pre– and post–operative patients' education and availability of such a regimen are something to be the considered to have a better outcome.

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