Pan Arab Journal of Oncology

Original Article

Adjuvant Chemotherapy in High Risk Colon Cancer Standard FOLFOX or XELOX versus Short Duration of XELOX

Amen H. Zaky[1*], Mayada F. Sedik[1], Maha S. Elnagar[2]

1. Medical oncology Department, South Egypt Cancer Institute, Assiut University.
2. Clinical oncology department, Faculty of Medicine, Assiut University

ABSTRACT

Background: Adjuvant chemotherapy for high risk colon cancer is mandotary in spite of high toxicity profile. But short duration of chemotherapy more privilege for patients and compliance. Aim of the study to compare short duration of adjuvant chemotherapy XELOX 4cycle (3 month arm) versus standard course of XELOX or FOLFOX (6 month arm)

Patients and Methods: High risk patients of colon cancer post radical surgery received adjuvant chemotherapy either 4cycles XELOX (3 month arm) versus standard course of XELOX or FOLFOX (6 month arm), comparing both group in toxicity profile, relapsing free survival and overall survival.

Result: Short duration of XELOX-4 arm showed more compliance significantly less in neuropathy and neutropenia in comparison to standard adjuvant course, and also without delay or reduction of chemotherapy dose. No significant difference between all groups in overall survival rate but **recurrence free Survival** significant higher recurrence in short course of adjuvant therapy XELOX-4 in comparison to standard course (8 month versus 15 month, P value 0.012) respectively.

Conclusion: Short duration XELOX adjuvant chemotherapy for high risk colon cancer is inferior to standard adjuvant therapy with high risk for recurrence

Keywords
colon cancer,
short duration,
adjuvant chemotherapy

INTRODUCTION

Adjuvant chemotherapy improves survival in patients with colon cancer. The success of six months multiagent combination therapy in the adjuvant treatment of colorectal cancer following complete surgical Resection became standard of care for high risk colon cancer (1,2).

Oxaliplatin based chemotherapy in combination either 5-fluorouracil + leucovorin (FOLFOX) or with capecitabine (XELOX) showed similar effect in adjuvant setting in improving survival and reduction of recurrence rate by 20% with similar effect and no overlapping toxicity (3,4). From the previous reports capecitabine containing ragmen (XELOX,) not inferior to FOLFOX but more tolerable to patient because no long time infusion and no hospital admission

Recently, there is a dilemma. About optimal duration of adjuvant chemotherapy in colon cancer, recent report showing that the 3 months regimen was as effective as the 6 months with a significantly lower toxicity (5,6). Additionally, in advanced colon cancer response to treatment achieved in a very short time and

prolonged treatment programs not enhance efficacy biologically (7). But recently corruption of previous reports was published about risk of short duration therapy in relapse rate especially to tumor burden and type of therapy which showed the results patients treated with XELOX, 3 months were as good as 6 months; for FOLFOX, 6 months added extra benefit (8,9)

We conduct this prospective randomized study to compare short course of adjuvant chemotherapy of capecitabine containing ragmen (XELOX,) for 3month only in high risk colon cancer versus standard course of chemotherapy (XELOX or FOLFOX) for 6 month respectively, Evaluating efficacy and toxicity profile in all group. Primary end point is relapsing free survival and secondary end point is overall survival

PATIENTS and METHOD

This study is a prospective randomized study aiming to compare short term for 4 courses capecitabine/oxaliplatin (XELOX4) 3 month arm with standard course for 6 month arm of adjuvant (FOLFOX or XELOX) as adjuvant treatment for colon carcinoma patients with stage III and high risk stage II (lymph node sampling<12; poorly differentiated tumor; vascular, lymphatic or perineural invasion, tumor presentation with obstruction or tumor perforation and pT4 stage) in terms of toxicity, relapsing-free survival (RFS) and overall survival. We exclude from study evidence of microscopic residual tumors, or previous history of chemotherapy or radiotherapy or any organ dysfunction

The study was conducted in South Egypt Cancer Institute as well as the Health Insurance Hospital starting from 2014 to 2018. Prospectively 240 patients enrolled in study receiving adjuvant chemotherapy for colorectal cancer, 88 patients received FOLFOX, 81 patients received XELOX for six month versus 71 patients received four cycles of XELOX for 3 months.

Safety assessment of patients after adjuvant therapy every 4 month by chest x rays and abdominal CT scan, and colonoscopy done after one year from radical surgery. Written informed consent was taken from all patients before enrolled to study and Ethical committee of south Egypt cancer Institute approved study.

Statistical methods

OS (overall survival), and RFS (recurrence free survival were calculated by Kaplan-Meier estimates with hazard ratios (Hr) and 95% Confidence interval analyzed using COX regression test . Chi-square Test analysis was used to compare the difference in proportions. Significance level is considered when $p \leq 0.05$

RESULTS

240 high risk colon cancers was enrolled in study, 71 received short term (XELOX-4) for 3 month arm and 169 patients received standard adjuvant including 88 patients FOLFOX and also 81 patients for XELOX for 6 month arm. No significance between both groups in age or sex, or pathological data and or in staging as seen and clarified in table (1).

Table 1. Baseline Demographic and Clinical Characteristics of standard duration of adjuvant XELOX and FOLFOX patient versus short duration of XELOX-4 adjuvant of high risk colon cancer

		Short duration XELOX-4 (n = 71)	Standard duration XELOX (n = 81)	Standard duration FOLFOX (n = 88)	P-value
Age in years	**Mean ± SD**	44.97 ± 12.1	43.32 ± 12.4	44.97 ± 12.1	0.412*
	Median (Range)	45 (23 - 70)	43 (26 - 70)	45 (18 - 70)	
Sex	**Male**	36(50.7%)	43 (53%)	48 (54.5%)	0.748**
	Female	35 (49.3%)	38 (46.9%)	40 (45.5%)	
Performance Status	**0**	39 (54.9%)	44 (54.3%)	48 (54.6%)	0.545**
	1-2	32 (45.1%)	37 (45.7%)	40 (45.4%)	
Primary Tumour Classification	**T1-2**	16 (22.5%)	18 (22.2%)	19 (21.6%)	0.433**
	T3	30 (42.2%)	35 (43.2%)	36 (40.9%)	
	T4	25 (35.3%)	28 (34.6%)	33 (37.5%)	
Regional LN Classification	**N0**	16 (22.5%)	18 (22.2%)	19 (21.6%)	0.478**
	N1	16 (22.5%)	19 (23.5%)	20 (22.7%)	
	N2	29 (40.8%)	32 (39.5%)	36 (40.9%)	
	N3	10 (14.2%)	12 (14.8%)	13 (14.7%)	
Grade	**I**	16 (22.5%)	18 (22.2%)	19 (21.6%)	0.075**
	II	30 (42.2%)	35 (43.2%)	36 (40.9%)	
	III	25 (35.3%)	28 (34.6%)	33 (37.5%)	
CEA Concentration	**Normal**	38 (53.5%)	42 (51.8%)	45 (51.1%)	0.545**
	Elevated	33 (46.5%)	39 (48.2%)	43 (48.9%)	
Pathology	**Adenocarcinoma**	39 (54.9%)	44 (54.3%)	48 (54.6%)	0.397**
	Mucinous	32 (45.1%)	37 (45.7%)	40 (45.4%)	

Short term therapy showed more compliance to treatment and very parentage of toxicity. Most of toxicity was hand and foot syndrome and peripheral neuropathy in (XELOX-4) short arm therapy but with significance lower in comparison to standard adjuvant course (FOLFOX group or XELOX) (p value 0.001 and 0.003 respectively). But Neutropenia and diarrhea was no significant difference between all groups (table2). Treatment related toxicity lead to withdrawal and delay or reduction of chemotherapy dose was significantly higher in standard adjuvant course (FOLFOX group or XELOX-6) than short duration course of adjuvant chemotherapy (XELOX-4) group (P value 0.001) which most of them related to Neuropathy and neutropenia (table 3).

No significance difference in Overall survival (OS) among all group was XELOX4=51%versus XELOX=61%, and FOLFOX=48%, Long rank P value 0.438, HR, 1.15; 95% CI, 1.19 to 1.49) (FIG.1). Regarding Relapsing free survival significance difference was (XELOX4=54% versus XELOX=92%, & FOLFOX=76% Long rank P value 0.01, hazard ratio [HR], 1.24; 95% CI, 1.05 to 1.46) (FIG.2). Cox regression analysis showed most factor affecting survival was Tumor stage including tumor size and lymph nod status (Table4).

Table 2. Most Common Treatment-related adverse events (all grades)

	XELOX-4 (n = 71)	XELOX-6 (n = 81)	FOLFOX (n = 88)	P-value*
Patients with at least 1 AE	2 (3.9%)	10 (19.6%)	17(19.3%)	0.002
Peripheral neuropathy	2 (3.9%)	14 (17.2%)	15 (17%)	0.003
Hand Foot Syndrome	2 (3.9%)	16 (19.7%)	10 (11.3%)	0.001
Neutropenia	2 (3.9%)	5 (6%)	10 (11.3%)	0.4
Diarrhoea	4 (7.8%)	8 (9%)	15 (17%)	0.381

***Chi-square Test analysis was used to compare the difference in proportions**
--Significance level is considered when p ≤ 0.05

Table 3. Treatment Modifications and Withdrawals

	XELOX 4 (n = 71)	XELOX 6 (n = 81)	FOLFOX (n = 88)	P-value*
Patients who received full no. of cycles	71 (100%)	70 (86.4%)	76 (86.2%)	0.17
Toxicity related withdrawal or modification	1 (1.4%)	11 (13.5%)	12 (13.6%)	**0.001**
Cycles with dose reduction (No. of patients with at least one dose reduction)	1 (1.4%)	11 (13.5%)	12 (13.6%)	**0.001**
Cycles with delays	1 (1.4%)	10 (12.3%)	10 (11.3%)	. **0.0001**

***Chi-square Test analysis was used to compare the difference in proportions**
--Significance level is considered when p ≤ 0.05

Table 4. Cox Hazard Regression of the Treatment associated Correlates

	P-value	HR*	95.0% CI**	
			Lower	Upper
Age	**= 0.015**	**1.146**	**1.095**	**1.989**
CTH (XELOX4 vs, XELOX6 vs. FOLFOX)	0.239	1.612	0.662	3.924
Primary Tumour Classification				
T1-2	1			
T3	**0.017**	**16.577**	**1.645**	**67.024**
T4	0.239	3.518	0.433	28.579
Regional LN Classification				
N0	1			
N1	0.786	1.168	0.230	54.578
N2	**0.010**	**31.346**	**2.288**	**49.365**
N3	0.489	2.288	0.230	21.578
CEA Concentration				
Normal	1			
Elevated	**0.016**	**1.856**	**1.094**	**4.397**
Chemotherapy				
No	1			
Yes	**0.032**	**1.754**	**1.050**	**2.929**

***HR=Hazard Ratio** ****CI=Confidence Interval**

Figure1: The overall survival of the Three groups

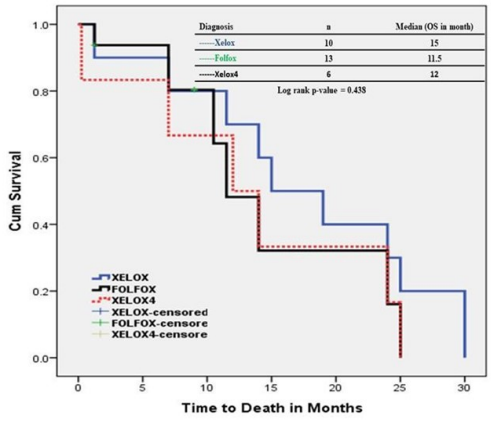

Fig. 1. The overall survival of the three groups

Figure 2: The Recurrence Free Survival of all groups

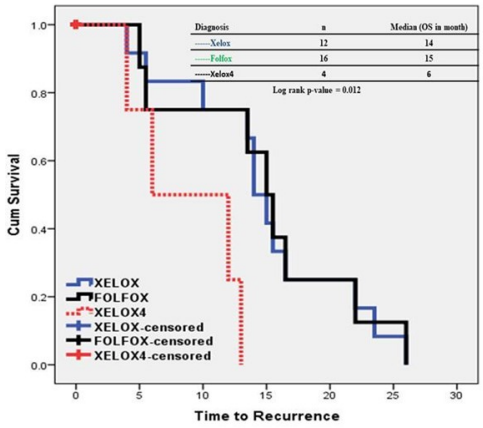

Fig. 2. The recurrence free survival of the three groups

DISCUSSION

Our study compare the short term of XELOX for 3 months therapy versus standard FOLFOX or XELOX regimen for 6 months in adjuvant setting of high risk colon cancer post radical surgery, which showed inferior of short term therapy of capecitabine containing regimen (XELOX,) with high risk of relapsing in comparison to standard regimen, but short term therapy more compliance to patients, no overlapping toxicity without delaying or reduction of dose in short term therapy

Adjuvant therapy is mandatory for high risk colon cancer which offered advantage in survival including DFS and OS and reduction in risk of relapsed disease by 20% especially in oxaliplatin based regimen (7,8,). All standard regimen containing oxaliplatin including with Capacitating (XELOX) or with 5-fluorouracil (FOLFOX) showed the similar efficacy and result with no difference in response or survival, but nearly the same efficacy between both group, the difference between both group in neuropathy and compliance to duration of treatment (4,10).

In our study showed, the short term XELOX regimen is more convenient to the patient than the prolonged infusion FOLFOX or XELOX, the privilege having tolerable side effects. Our study has proved that short term XELOX is as efficient and safe drug in toxicity profile when compared with standard FOLFOX in adjuvant setting of high risk colon cancer. Short term adjuvant therapy of XELOX-4 significantly decreased incidence of toxicity in form of peripheral neuropathy, neutropenia, hand foot syndrome than previously reported and in comparison to standard FOLFOX or XELOX group (11,12),which make it more convenient to the patients and keeps regularity of cycles without delay or reduction of the dose and this result compatible with recent reports (11).

The overall survival XELOX4=51% 12 month versus XELOX=61%, 15 month and FOLFOX=48%, 11.5 month**,** Long rank P value 0.438) respectively. The difference was statistically non-significant. While the RFS was (XELOX4=54% 6month versus XELOX=92% 14month & FOLFOX=76% 15month, Long rank P value 0.01) respectively. The difference was statistically significant, very important focus about no similarity of survival of short term therapy to standard therapy with high risk of recurrence and depends on tumor size and nodal status by regression analysis. In comparable for previous reports about capacitabin containing regimen of short term therapy worse RFS (8,9) and choice must be balanced according to tumor burden and lymph node level affection. All the previous data had an important impact which clearly on reducing on duration of adjuvant treatment which particularly relevant to patients and improving toxicity profile by which reflecting in quality of life to complete the treatment without delay or discontinuation but we need that without affecting on survival benefit which must be the scope in future research.

CONCLUSION

Short duration XELOX adjuvant chemotherapy for high risk colon cancer is inferior to standard adjuvant therapy with high risk for recurrence.

Compliance with Ethical Standards:

•Conflict of interest: Author Amen H zaky declares that he has no conflict of interest. Author Myada F.Sedik declares that she has no conflict of interest. Author Maha S.Najar declares that she has no conflict of interest.

•All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

•Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Labianca R, Nordlinger B, Beretta GD et al. Early colon cancer: ESMO clinical practice guidelines. Ann Oncol 2013; 24(Suppl. 6): vi64–vi72
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. V.2.2017
3. Graham JS, Cassidy J. Adjuvant therapy in colon cancer. Expert Rev Anticancer Ther. 2012;12:99–109
4. Haller DG, Tabernero J, Maroun J, de Braud F, Price T,

Van Cutsem E, et al.Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29:1465–71.
5. Andrè T, Iveson T, Labianca R et al. The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration: prospective combined analysis of phase III trials investigating duration of adjuvant therapy with the FOLFOX (FOLFOX4 or Modified FOLFOX6) or XELOX (3 versus 6 months) regimen for patients with stage III colon cancer: trial design and current status. Curr Colorectal Cancer Rep 2013;9: 261–269.
6. Phase III trial comparing 3–6months of adjuvant FOLFOX4/XELOX in stage II–III colon cancer: safety and compliance in the TOSCA trial. S. Lonardi1,‡, A. Sobrero2,‡, G. Rosati3, M. Di Bartolomeo4, M. Ronzoni5, G. Aprile6, M. Scartozzi7,M. Banzi8, M. G. Zampino9, F. Pasini10, P. Marchetti11, M. Cantore12, A. Zaniboni13, L. Rimassa14,L. Ciuffreda15, D. Ferrari16, S. Barni17, V. Zagonel1, E. Maiello18, E. Rulli19 & R. Labianca20*, On Behalfof TOSCA (Three or Six Colon Adjuvant) Investigators. Annals of Oncology 27: 2074–2081, 2016
7. -Hochster HS, Grothey A, Hart L et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONcePT. Ann Oncol 2014; 25:1172–1178.
8. Three Versus 6 Months of Oxaliplatin-Based Adjuvant Chemotherapy for Patients With Stage III Colon Cancer: Disease-Free Survival Results From a Randomized, Open-Label, International Duration Evaluation of Adjuvant (IDEA) France, Phase III Trial. Thierry André, Dewi Vernerey, Laurent Mineur, Jaafar Bennouna, Jérôme Desrame, Roger Faroux.J Clin Oncol. 2018 May 20;36(15):1469-1477
9. FOLFOX or CAPOX in Stage II to III Colon Cancer: Efficacy Results of the Italian Three or Six Colon Adjuvant Trial. Alberto Sobrero, Sara Lonardi, Gerardo Rosati, Maria Di Bartolomeo, Monica Ronzoni, Nicoletta Pella, Mario Scartozzi, Maria Banzi, Maria Giulia Zampino, Felice Pasini, Paolo Marchetti, Maurizio Cantore, Alberto Zaniboni, Lorenza Rimassa, Libero Ciuffreda, Daris Ferrari, Vittorina Zagonel, Evaristo Maiello, Sandro Barni, Eliana Rulli, and Roberto Labianca, on behalf of the TOSCA Investigators. J Clin Oncol. 2018 May 20;36(15):1478-1485
10. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. Lancet. 2007;370:2020–9.
11. Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ,et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses.J Clin Oncol.2011;29:3768–74.
12. Capecitabine plus Oxaliplatin (XELOX) versus FOLFOX4 as adjuvant therapy forColon Cancer.Ibtessam S. Eldeen,MD; Noha Y. Ibrahim, MD; Dalia O. Darwish, MD; Wael S. Makar, *MD*. Austral - Asian Journal of Cancer ISSN-0972-2556, Vol. 11, No. 3, July 2012
13. Storey D. J.,Sakala M, McLean C.M, Phillips H.A ,Dawson L.K,Wall L.R, Fallon M.t and Clives: Capecitabine combined with oxaliplatin (CapOx) in clinical practice: how significant is peripheral neuropathy? Annals of Oncology Volume21,Issue8. Pp. 1657-1661. Apr 2011