ORIGINAL ARTICLE ◄

Capecitabine plus Oxaliplatin (XELOX) versus FOLFOX4 as adjuvant therapy for Colon Cancer

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Abstract

Background: Adjuvant chemotherapy improves overall survival (OS) in patients with locally advanced, node-positive (stage III) colon cancer.
Methods: This study was designed to compare capecitabine/oxaliplatin (XELOX) with FU/LV/oxaliplatin (FOLFOX4) as adjuvant treatment for patients with high risk stage II and stage III colon carcinoma in terms of toxicity, patient convenience, event-free survival (EFS) and overall survival. Patients were followed up for a median period of 39 months ranging from 30 to 48 months.
Results: Sixty four patients were enrolled in each arm. The overall survival at 36 and 48 months for the XELOX group was 73.8% and 62% respectively. While the overall survival for FOLFOX group was 72% and 58% respectively (HR 0.8338, 95%CI= 0.2557-2.719). The difference was not statistically significant. Grade 3/4 neutropenia was more significant with FOLFOX 22% versus 9.4% (p=0.01). XELOX was associated with more G3/4 diarrhea 17.2% versus 11% (p=0.25), and hand and foot syndrome 9.4% versus 1% (p=0.04).
Conclusion: This study reveals that XELOX is as effective and safe as FOLFOX and has a manageable tolerability profile in the adjuvant setting with more convenience to the patients.

Introduction

Adjuvant chemotherapy improves overall survival (OS) in patients with locally advanced, node-positive (stage III) colon cancer. The success of multiagent combination therapy in the treatment of metastatic colorectal cancer had lead to testing such regimens in the adjuvant setting[1].

Oxaliplatin, is an important chemotherapeutic agent in metastatic colorectal cancer and has been shown to prolong disease-free survival significantly when added to fluorouracil/ leucovorin (FU/LV) in patients with stage II/III colon cancer, with reduction in recurrence rate of 21% and 23% reported in two large trials[2].

Capecitabine (Xeloda) is an oral fluoropyrimidine that has established efficacy in the treatment of metastatic colorectal cancer and as a single-agent in the adjuvant treatment. In both settings, capecitabine has shown improved tolerability with the convenience of being an oral chemotherapy[3-5].

Capecitabine/ oxaliplatin in combination have proved efficacy with no major overlapping toxicity in patients with stage III colorectal cancer in different randomized studies[6-7].

This study was conducted in Kasr Al Aini centre of oncology and nuclear medicine as well as in the health insurance clinic in the period from January 2007 till December 2008 to compare the safety and efficacy of adjuvant capecitabine plus oxaliplatin (XELOX) to oxaliplatin/ FU/LV (FOLFOX4), the standard regimen in stage III colon cancer at study initiation.

Sixty four patients in the XELOX arm were compared with 64 patients in the FOLFOX arm. The final analysis was performed in January 2011, 24 months after all enrolled patients had completed the study treatment.

Patients and Methods

Eligibility Criteria

- Patients ≥ 18 years old
- Histologically confirmed stage II (High risk patients) and III colon carcinoma (Dukes' stage C)
- Eastern Cooperative Oncology Group performance status score of 0 or 1.
- Adequate hematologic, renal and hepatic functions.

Baseline Assessment

Patient history and physical examination, ECOG performance status, chest x-ray, carcinoembryonic antigen analysis and postoperative CT chest, abdomen and pelvis were done. Hematology and blood chemistry (including creatinine clearance calculation) were assessed before treatment.

Study Design and Treatment

The study was designed to compare capecitabine/oxaliplatin (XELOX) with FU/LV/oxaliplatin (FOLFOX4) as adjuvant treatment for patients who have undergone surgery for high risk stage II(lymph node sampling<12; poorly differentiated tumour; vascular, lymphatic or perineural invasion, tumour presentation with obstruction or tumour perforation and pT4 stage), and stage III colon carcinoma in terms of toxicity, patient convenience, event-free survival

(EFS) and overall survival. Patients were followed up for a median period of 39 months ranging from 30 to 48 months.

The XELOX regimen consisted of a 2-hour intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 and oral capecitabine 1,000 mg/m^2 twice daily given for 14 days of a 3-week cycle, for a total of eight cycles (24 weeks). The first dose of capecitabine was given on the evening of day 1 and the last dose on the morning of day 15 of each cycle.

The FOLFOX4 consisted of oxaliplatin 85mg/m^2 i.v. over 2 h, day 1 and 15 combined with leucovorin 200mg/ m^2 over 2h followed by FU bolus 400mg/ m^2 and then FU 600mg/ m^2 2h infusion day 1 and day 2 repeated on day 15 for a total of six cycles (24 weeks).

Dose modification of oxaliplatin to 100 mg/m^2 was performed for grade 3/4 nausea or vomiting, grade 4 stomatitis, and for paresthesias with pain.

Adverse events

Adverse events were monitored continuously during treatment and 28 days after last administration of chemotherapy. The intensity of adverse events and laboratory parameters were graded according to the NCI Common Toxicity Criteria for Adverse Events, version 3.0.

A complete laboratory assessment was done before each treatment cycle. The following parameters were monitored: AST, ALT, alkaline phosphatase, albumin, bilirubin (total and direct), serum creatinine, and complete blood count.
The safety profile and the efficacy of the XELOX regimen was compared with that of the FOLFOX regimen.

Statistical Methods

The cutoff date for the present study was June 2011. DFS and OS were analyzed using Cox proportional hazards regression models and presented as Kaplan-Meier estimates with hazard ratios (HR) and 95% CI. Study treatment arms were compared using a two-sided log-rank test. Planned multivariate analyses of toxicity, patient convenience, DFS and OS were performed using stratification variables. Planned subgroup analyses and a planned analysis of the effect of dose modifications on DFS were also performed.

Results

This study was conducted at the Kasr Al Aini centre of oncology and nuclear medicine as well as in the health insurance clinic in the period from January 2007 till December 2008 to compare the safety and efficacy of adjuvant capecitabine plus oxaliplatin (XELOX) to oxaliplatin/FU/LV(FOLFOX4), in high risk stage II and stage III colon cancer at study initiation.

Sixty four patients in the XELOX arm were compared with 64 patients FOLFOX arm. The final analysis was performed in January 2011; 24 months after all enrolled patients have completed the treatment.

Patient characteristics were well matched between the two treatment groups, with a median age of 53 years in the XELOX arm and 56 years in the FOLFOX arm. The major tumor classification was T3 in both arms with 84% in the XELOX and 87% in the FOLFOX arms. As regards the regional lymph nodes in the XELOX arm, 53% were N1 and 25% were N2, while in the FOLFOX arm 47% were N1 and 28% were N2. CEA was above normal in 6% and 9% in the XELOX and FOLFOX arms respectively, (Table 1).

The number of patients who completed full number of cycles was 38 in the XELOX arm versus 40 patients in the FOLFOX arm (59.4% and 62.5% respectively). Patients who did not complete the treatment were related to toxicity or lost follow up. Toxicity related withdrawal was 31.3% and 29.7% in XELOX and FOLFOX arms respectively.

Dose reductions were done in 37.5% (24 patients) in the XELOX arm, compared to 34.4% (22 patients) in the FOLFOX arm. Cycle delays due to neutropenia, anemia or gasterointestinal toxicities were required in 51% and 56% in the XELOX and FOLFOX arms respectively. None of these treatment modifications comparisons were statistically significant, (Table 2).

Adverse events associated with XELOX versus FOLFOX according to the NCI toxicity criteria is shown in tables 3 and 4. The overall rates of adverse events were more or less similar in both groups, except for G3/4 neutropenia in FOLFOX arm was 22%(14 patients) versus 9.4% (6 patients) in the XELOX arm. XELOX was associated with more G3/4 diarrhea 17.2% versus 11%, and hand and foot syndrome 9.4% versus 1%.

The overall survival at 36 and 48 months for the XELOX group was 73.8% and 62% respectively. While the overall survival for FOLFOX group was 72% and 58% respectively (HR 0.8338, 95%CI= 0.2557-2.719). The difference was not statistically significant (fig 1).

The event free survival at 36 months was 69% and 67% for the XELOX and FOLFOX groups respectively. While the EFS at 48 months was 58% and 57% for XELOX and FOLFOX groups respectively *(HR 0.8574, 95% CI= 0.2891-2.543)*. The difference was statistically non significant (fig. 2).

Discussion

The XELOX regimen is more convenient to the patient than the prolonged infusion FOLOX. There is no hospital admission with the privilege of being an oral drug and having tolerable side effects. Our study has proved that XELOX is as efficient and safe when compared with FOLFOX4 in stage III and high risk stage II colon cancer.

Peripheral neuropathy was similar in the two groups. This was also evident by *Storey et al 2010* who found that acute peripheral neuropathy during XELOX appears similar to FOLFOX4 but chronic peripheral neuropathy in adjuvant patients more than 6 months may be more prevalent with XELOX. Hand-foot syndrome was more common with XELOX compared with FOLFOX (18.7% vs 9.4% (p= 0.15) but the rate was lower than in previous monotherapy trials.

The incidence of grade 3/4 diarrhea and neutropenia was 17.2% and 4.6% for XELOX and 11% and 22% for the FOLFOX cases respectively. The incidence of neutropenia was significantly less in the XELOX patients (p= 0.01). This was less than that reported from *LU et al 2010,* who reported also more grade 3/4 neutropenia in the FOLFOX4 arm versus the XELOX arm, 31.6% and 14.3% respectively (P = 0.039), while XELOX showed more grade 3/4 thrombocytopenia (19.0% vs. 6.6%, P = 0.038) and hand-foot syndrome (11.9% vs. 1.3%, P = 0.012).

The rate of hand-foot syndrome in the present trial (all grades, 18.7%; grade 3& 4, 9.4%) is considerably lower than that reported with capecitabine monotherapy (62%; 18%) [8]. This reduced rate is likely due to the 20% lower dose of capecitabine in the XELOX regimen versus standard-dose monotherapy. This was compared with 9.4% cases of hand and foot syndrome in the FOLFOX group with 1% grade 3 to 4 which was significant ***(P= 0.04)***.

In regards to thrombocytopenia, 12.5% of the patients developed thrombocytopenia in the XELOX group versus 14% in the FOLFOX group. Of these 8% and 1.5% were grade 3 to 4 which was statistically significant ***(p= 0.06)***. A Chinese study done by *LU et al 2010* on XELOX showed more grade 3/4 thrombocytopenia (19.0% vs. 6.6%, P = 0.038) and hand-foot syndrome (11.9% vs. 1.3%, P = 0.012) in comparison with FOLFOX4.

In this study the incidence of diarrhea was 60% with 17.2% being grade 3 to 4 in XELOX arm. This was higher than patients receiving FOLFOX4, 53.1% and 11% respectively however it did not reach statistical significance for grade 3 to 4 **(p= 0.25** *)*. This is consistent with *Arkenau et al 2008*, that showed higher incidence of thrombocytopenia , diarrhea and hand and foot syndrome with less neutropenia with XELOX when compared with infusional fluouracil/leucovorin in patients with metastatic colorectal cancer.

As for neutropenia, it was less in the XELOX patients as compared with the FOLFOX 18.7% vs 31.3% (p= 0.09). Grade 3 to 4 neutropenia were 4.6 and 22% respectively which was statistically significant ***(p= 0.01).***

In our study, hand and foot syndrome, thrombocytopenia as well as grade 3 to 4 diarrhea were more common in the XELOX patients. Neutropenia was less than what was seen in the FOLFOX regimen. This was consistent with ***Cassidy et al 2008.***

The overall survival at 36 and 48 months for the XELOX group was 73.8% and 62% respectively. While the overall survival for FOLFOX group was 72% and 58% respectively (HR 0.8338, 95%CI= 0.2557-2.719).

The event free survival at 36 months was 69% and 67% for the XELOX and FOLFOX groups respectively. While the EFS at 48 months was 58% and 57% for XELOX and FOLFOX groups respectively *(HR 0.8574, 95% CI= 0.2891-2.543)*. The difference was statistically non significant.

There were several limitations in our study, being a single centre non randomized study. Data depended on the accuracy of medical notes and the grading of side effects may have been underestimated. Concurrent co-morbidity such as diabetes which is associated with higher rates of neuropathy during chemotherapy was not accurately correlated.

In conclusion, this study reveals that XELOX is as effective and safe as FOLFOX and has a manageable tolerability profile in the adjuvant setting with more convenience to the patients.

Tables

Table 1: Baseline Demographic and Clinical Characteristics of XELOX and FOLFOX patients

Characteristic	XELOX (n = 64)		FOLFOX (n = 64)	
	N0	%	N0	%
Age, years				
Median	53		56	
Range	28-69		27-68	
Sex				
Male	28	44	29	45
Female	36	56	35	55
ECOG performance status				
0	48	75	50	78
1	16	25	14	22
Primary tumor classification				
T1-2	2	3	3	5
T3	54	84	56	87
T4	8	13	5	8
Regional lymph nodes classification				
N0	14	22	16	25
N1	34	53	30	47
N2	16	25	18	28
Histologic appearance				
Well differentiated	2	3	4	6
Moderately differentiated	61	95.3	60	94
Poorly differentiated	1	1.5	0	0
CEA concentration				
Normal	60	94	58	91
Above Normal	4	6	6	9

Table 2: Treatment Modifications, and Withdrawals

Parameter	XELOX		FOLFOX	
	N0	%	N0	%
Patients who received full no. of cycles	38	59.4	40	62.5
Toxicity related withdrawal	20	31.3	19	29.7
Cycles with dose reduction (N0 of patients with at least one dose reduction)	24	37.5	22	34.4
Cycles with delays	33	51	36	56

Table 3: Most Common Treatment-Related adverse events (all grades)

Events	XELOX		FOLFOX		P value
	N0	%	N0	%	
Patients with at least 1 AE	58	91	60	93.8	0.45
Nausea	34	53.1	36	56.3	0.65
Diarrhea	38	60	34	53.1	0.35
Vomiting	26	40.6	28	43.8	0.4
Fatigue	19	30	22	34.4	0.65
Hand-foot syndrome	12	18.7	6	9.4	0.15
Neutropenia	12	18.7	20	31.3	0.15
Thrombocytopenia	11	17.2	4	6.3	**0.05***
Anorexia	11	17.2	14	22	0.3
Stomatitis	13	20.3	15	23.4	0.65
Abdominal pain	8	12.5	9	14	0.9
Peripheral neuropathy	7	11	8	12.5	0.7

* P value<0.05 is statistically significant

Table 4: Treatment-Related Grade 3/4 adverse events

Events	XELOX		FOLFOX		P value
	N0	%	N0	%	
Diarrhea	11	17.2	7	11	0.25
Peripheral neuropathy	5	8	4	6.3	0.6
Neutropenia	3	4.6	14	22	**0.01***
Vomiting	4	6.3	4	6.3	>1
Nausea	3	4.6	4	6.3	0.5
Hand-foot syndrome	6	9.4	1	1.5	**0.04***
Thrombocytopenia	5	8	1	1.5	**0.06***
Stomatitis	2	3	2	3	>1
Abdominal pain	3	4.6	3	4.6	>1

* P value<0.05 is statistically significant

Figures

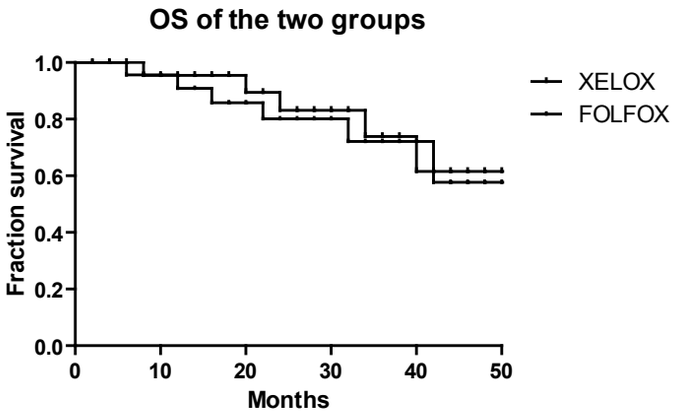

Fig1: The overall survival of the two groups

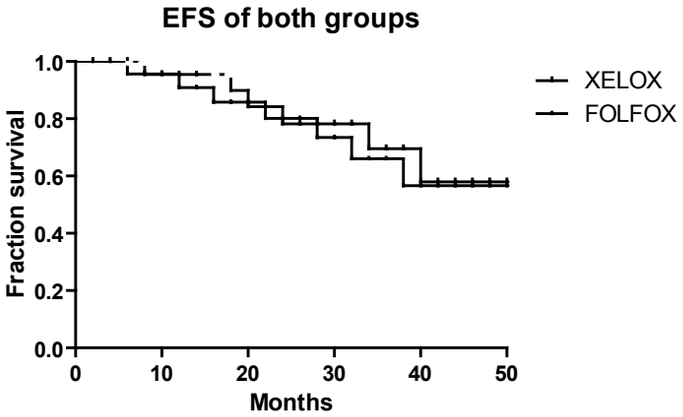

Fig2: The event free survival of both groups

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