Journal of BUON **16:** 682-688, 2011

ORIGINAL ARTICLE

The toxicity and efficacy of Nordic-FLOX regimen as adjuvant treatment of stage III colon cancer

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Summary

Purpose: *To evaluate the toxicity and efficacy of oxaliplatin combined with the Nordic regimen of bolus 5-fluorouracil (5-FU) and leucovorin (LV) (Nordic-FLOX) as adjuvant treatment in stage III colon cancer patients.*

Methods: *Fifty-three patients with resected stage III colon cancer were treated with adjuvant bolus Nordic-FLOX regimen (oxaliplatin 85 mg/m^2 on day 1, bolus 5-FU 500 mg/m^2 and bolus LV 60 mg/m^2 days 1 and 2) every 2 weeks for 12 cycles.*

Results: *The probability of disease-free survival (DFS) at a median follow-up time of 29 months was 72%. Relapse was seen in 13 (24.5%) patients. The probability of 3-year overall survival (OS) at 36 months was 85%. Grade IV neutropenia was noticed in 15.1% of the patients, grade III-IV neurotoxicity was not encountered, while grade II neurotoxicity was 17%. Gastrointestinal toxicity (mild diarrhea) was seen in 11.3% of the patients.*

Conclusion: *Adjuvant treatment of stage III colon cancer with the Nordic-FLOX regimen can be an alternative regimen to infusional and other bolus regimens due to its easy administration, lower toxicity, and similar efficacy.*

Key words: adjuvant treatment, colon cancer, efficacy, Nordic-FLOX regimen, toxicity

Introduction

Colorectal cancer (CRC) is a common and potentially lethal disease. Approximately 146,970 new cases of CRC are diagnosed each year in the United States, of which 106,100 are colon cancer [1]. Surgery is the primary treatment for early-stage colon cancer (stages I-III). Unfortunately occult micrometastases present at the time of surgery can colon cancer to disease recurrence. For this reason the main aim of adjuvant (or postoperative) chemotherapy is to eradicate micrometastases and to increase DFR and OS.

5-FU-based adjuvant chemotherapy had became the main treatment in stage III patients over the past years. The combination of 5-FU and levamisole demonstrated a significant survival benefit in the INT-0035 trial and this study was the first to prove the role of 5-FU-based chemotherapy in a large number of patient population [2]. After the results of the studies of Wolmark et al. and O'Connell et al. 5-FU-LV combination was found to be an effective adjuvant treatment in the late 1990's [3,4]. Because better efficacy of oxaliplatin and 5-FU-LV combination was demonstrated in advanced CRC patients [5-7], it was also studied in the adjuvant setting in stage II-III colon cancer in randomized trials. The benefits of adjuvant chemotherapy have been shown in a randomized phase III trial (MOSAIC), which was the first large-scale trial comparing oxaliplatin-infusional 5-FU-LV combination (FOLFOX4) with infusional 5-FU-LV only. DFS and OS were significantly better in the FOLFOX4 group compared to 5-FU-LV, especially in patients with stage III (node-positive) disease (5-year DFS 66.4 vs. 58.9%, p=0.005; 6-year OS 72.9 vs. 68.7%, p=0.023). Also some benefit was seen in high risk stage II patients [8]. Also another more recent large randomized

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Received 24-03-2011; Accepted 21-04-2011

trial, (NSABP C-07), compared oxaliplatin and bolus 5-FU-LV combination (FLOX) with bolus 5-FU-LV (Roswell Park regimen) only. Approximately similar results were found in this study; 3-year DFS was 76.1 vs. 71.8% (p= 0.0034) [9].

After these randomized trials, adjuvant chemotherapy is recommended for patients with stage III and high risk stage II patients (inadequate lymph node dissection, T4 tumor, high grade, vascular invasion, presentation with bowel obstruction/perforation). The accepted regimen for adjuvant chemotherapy of colon cancer patients is FOLFOX4 [10]. However, enough data show that FLOX, as a bolus regimen, is as effective as infusional FOLFOX4. The Nordic schedule of oxaliplatin combined with 5-FU-LV is another bolus regimen which had been studied and found to be effective in patients with metastatic CRC [11].

In the present report, the results of 53 patients with stage III colon cancer that were treated with Nordic-FLOX regimen are presented.

Methods

Patients

Fifty-three patients who were diagnosed with stage III colon cancer (any T, N+, M0) and treated with the Nordic-FLOX regimen between July 2006 - July 2009 were retrospectively assessed. The age range was 18-75 years (median 56.8) and ECOG performance status < 2 (range 0-2).

Treatment protocol

Adjuvant chemotherapy was administered within 4-6 (at least 3) weeks after the operation. Before each chemotherapy cycle, an infusion of 500 ml 0.9% NaCl containing one ampoule $MgSO_4$ (1.5 g) and calcium gluconate (225 mg) were given. Then 3 mg granisetron or 4 mg ondansetron were administered as 5-min i.v. infusion for emesis prevention. Patients received bolus 5-FU 500 mg/m^2 at first, then bolus LV 60 mg/m^2. After 5-FU-LV, oxaliplatin 85 mg/m^2 was given as a 2-h infusion on day 1. 5-FU and LV were repeated on day 2. The treatment cycles were repeated every 14 days. The planned cumulative dose for oxaliplatin was 1020 mg/m^2, for 5-FU 12.000 mg/m^2 and for LV 1440 mg/m^2.

Assessment of toxicity and efficacy

The toxicities experienced during treatment were graded according to WHO Toxicity Criteria [12]. In each cycle, treatment was delayed with neutrophil count <1800/mm^3, leucocyte (WBC count) < 4000/mm^3, platelet count <100000 mm^3, Hb <9 g/dl, ALT ≥2 the upper limit of normal.

For patients with grade I neutropenia or leukopenia, or grade I thrombocytopenia on the day of treatment, chemotherapy was delayed for one week and was administered in the same dosage in patients with normal levels in the next week. The dose of oxaliplatin and 5-FU was reduced by 20% in cases with persisting grade I/II thrombocytopenia for ≥ 2 weeks after the normalisation of the platelets' count. We used G-CSF prophylaxis after the next cycle in patients with persisting grade I/II neutropenia/leukopenia for ≥ 2 weeks or in those who had experienced grade III/IV neutropenia or leukopenia at any time. For patients who developed grade III/IV neutropenia/leukopenia for second time despite G-CSF prophylaxis, we decreased both oxaliplatin and 5-FU dosage by 20%.

In case of persisting grade II neurotoxicity between cycles, a 25% reduction in the total dose of oxaliplatin was made. We delayed a chemotherapy cycle and reduced the dose of oxaliplatin by 20% for the next cycle in patients with grade II thrombocytopenia. Also chemotherapy was delayed and a 20% dose reduction of 5-FU and oxaliplatin was made in the next cycle in patients with serum level of ALT/AST ≥ 2.5-5 × upper limit of normal.

The primary efficacy endpoint was DFS, defined as the time from diagnosis (operation time) to relapse or death from any cause, or last visit without evidence of disease recurrence. Secondary endpoint was OS, defined as the time from study enrollment until the last visit or death.

Follow-up

The follow-up time was defined as the number of months from enrollment (operation time) until the last visit.

After the end of treatment the patient follow-up was done every 3-6 months and included physical examination, full blood count, serum biochemistry and serum carcinoembryonic antigen level (CEA), chest radiography and abdominal ultrasound for the first 2 years and every 6 months thereafter for a total of 5 years. Control colonoscopy was performed one year after diagnosis, CT imaging every 6 months or every year. Disease recurrence was detected by imaging, or biopsy (for local relapse by colonoscopy). Elevation of serum CEA was also helpful for confirmation of recurrence, but CEA elevation alone without any imaging findings was not accepted as recurrence.

Statistical analysis

All of the calculations were performed by using the SPSS-17 statistical programme. Descriptive analysis was used to define the means, medians of numerical values and to show the ratios of toxicity grades. Also the relations between parameters were performed using Crosstabs and Fisher's exact test. The statistical significance was defined with a p-value of < 0.05. The probability of DFS and OS was estimated using the Kaplan-Meier method.

Results

Patient characteristics

Fifty-three patients who were diagnosed with stage III colon cancer between July 2006 and July 2009 were enrolled. There were 26 (49.1%) females and 27 (50.9%) males with median age 56.8 years (range 26-75). Median follow-up was 28.8 months (range 14.7-52). The patients received 12 courses of chemotherapy (approximately for 6 months), except one patient who received only 3 courses because of early brain metastasis. This patient's operation was incomplete with positive surgical margin.

The histological type was compatible with adenocarcinoma with mucinous component in 6 of 53 (11.3%) patients. Histological grade was poor in 6 (11.3%) patients and undifferentiated in 1 (1.9%). Surgical margin was negative in 38 (71.7%) patients, while it was microscopically positive (R1) in 13 (24.5%) patients and R2 in 2 (3.8%). Vascular invasion was seen in 16 (30.2%) patients. Fourteen patients presented with acute abdominal pain (bowel obstruction). Most of the patients had T3 disease (n=43; 81.1%); T1-T2 were seen in 1 patient each (1.9%), and only 8 (15.1%) of the patients had T4 (Table 1).

Table 1. Patient and disease characteristics

Characteristics	*Number of patients*	*%*
Age (years)		
≤60	28	52.8
>60	25	47.2
Sex		
Male	27	50.9
Female	26	49.1
Primary tumor		
T1	1	1.9
T2	1	1.9
T3	43	81.1
T4	8	15.1
Primary tumor localization		
Caecum	7	13.2
Ascending colon	4	7.5
Hepatic flexure	2	3.8
Transverse colon	6	11.3
Splenic flexure	4	7.5
Descending colon	9	17
Sigmoid	21	39.6
Acute abdominal pain		
Obstruction	14	26.4
No obstruction	39	73.6
Histological differentiation		
Well	4	7.5
Moderate	42	79.2
Poor	6	11.3
Undifferentiated	1	1.9
Histological type		
Adenocarcinoma	46	86.8
With mucinous component	6	11.3
Signet ring	1	1.9
Surgical margin		
R0	38	71.7
R1	13	24.5
R2	2	3.8
Lymph node involvement		
1-4	36	67.9
>4	17	32.1
Vascular invasion		
Yes	16	30.2
No	37	69.8

Efficacy

Thirteen patients relapsed; 4 of them had R1 and one had R2 surgical margins. Liver was the leading metastatic site (6/13; 46.1%). Brain and bone metastases were seen in only one patient each. Sigmoid colon region was the leading primary region in most patients. Metastases were seen in T3 and T4 patients. The histological type was compatible with adenocarcinoma with mucinous component in 2 of them. Lymph node involvement was higher in patients that had relapsed and this was statistically significant (Table 2). The probability of DFS at 36 months was 72% (Figure 1). Five patients died because of disease. The earlier death happened 16.7 months and the last 41.1 months after the operation. The mean OS at a median of 29 months follow-up time (range 16-51) was 47.8 months (95% CI 44.3-51.2), and the probability of survival at 36 months was 85% (Figure 2).

Toxicity

No anemia was observed in 37 (69.8%) patients, while grade I and II anemia was seen in 13 (24.5%) and 3 (5.7%) patients, respectively. Grade III leukopenia was observed in only 2 patients (3.8%) and grade IV neutropenia was seen in 8 (15.1%) patients. Although grade IV neutropenia was observed in 8 patients, no

Table 2. Characteristics of patients with relapse

Characteristics	*Number of patients*	*%*
Gender		
Male	9	69.3
Female	3	30.7
Bowel obstruction/perforation		
Present	4	30.7
Absent	9	69.3
Histological type		
Adenocarcinoma	11	84.6
With mucinous component	2	15.4
Signet ring	0	0
Histological differentiation		
Well	0	0
Moderate	8	61.5
Poor	5	38.5
T stage		
T1	0	0
T2	0	0
T3	9	69.3
T4	3	30.7
N stage		
N0	5	38.4
N1	5	38.4
N2	3	23.2
Vascular invasion		
Yes	7	53.8
No	6	46.2
Surgical margin		
R0	8	61.5
R1	4	30.7
R2	1	7.6
Metastatic site		
Liver only	4	30.7
Lung only	3	23
Liver+lung+lymph node	2	15.3
Lymph node+bone	1	7.6
Brain only	1	7.6
Peritoneal carcinomatosis	2	15.3

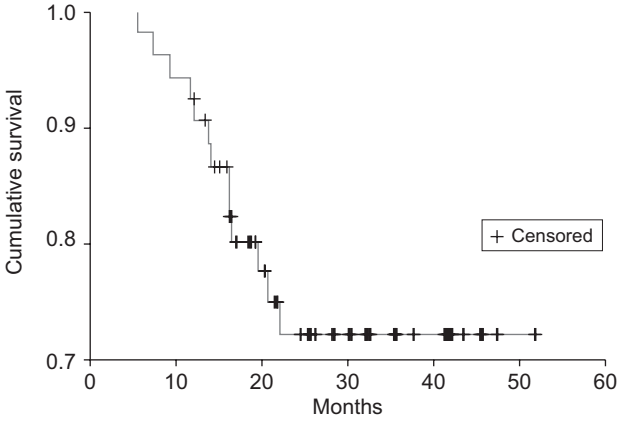

Figure 1. Patient disease-free survival.

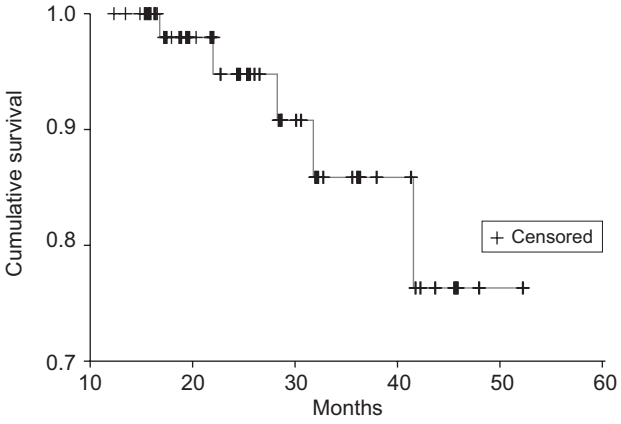

Figure 2. Patient overall survival.

neutropenic fever and severe diarrhea with neutropenia were encountered in any of these patients. Grade I-II thrombocytopenia was noted in 15% of the patients. Grade II liver dysfunction was seen in 3 (5.7%) patients. Only grade I oral mucositis was registered in 5 (9.4%) patients. The rate of mild diarrhea was approximately 19%. Grade I renal dysfunction was seen in one patient. Grade I emesis was seen in 66% of the patients and grade III in only 1 patient. Grade III neurotoxicity was not seen in any of the patients while grade II peripheral neuropathy was seen in only 9 (17%) patients (Table 3).

Thirty-four patients had dose modifications because of toxicity. The most frequent reason for dose reduction was cytopenia (8 patients with grade III neutropenia, 8 with grade IV neutropenia, 2 with grade III leukopenia, and 3 with grade II thrombocytopenia).

Table 3. Toxicity of Nordic-FLOX regimen in our study

Toxicity	*Grade I* *%*	*Grade II* *%*	*Grade III* *%*	*Grade IV* *%*
Anemia	24.5	5.7	0	0
Neutropenia	22.6	13.2	15.1	15.1
Thrombocytopenia	22.6	5.7	0	0
Diarrhea	7.5	11.3	0	0
Nausea	66	7.5	1.9	0
Stomatitis	9.4	0	0	0
Hepatotoxicity	11.3	5.7	0	0
Renal	1.9	0	0	0
Neuropathy	39.6	17	0	0

Table 4. Comparison of toxicity profile of FLOX, FOLFOX and Nordic-FLOX regimens

Toxicity	*FLOX*[1] *%*	*FOLFOX*[2] *%*	*Nordic- FLOX*[3] *%*	*Our study %*
Grade III neutropenia	8.1	41	32	15.1
Grade IV neutropenia	2.4	12.3	26	15.1
Grade III diarrhea	38	10.8	7	0
Grade I neuropathy	52.1	48.2	Not reported	39.6
Grade II neuropathy	19.8	31.6	41	17
Grade III neuropathy	8.2	12.4	13	0
Nausea	15.6	5.1	6	7.5

[1]NSABP C-07 study [9], [2]MOSAIC [13], [3]Phase II trial of Nordic-FLOX in advanced colorectal cancer [11]

Table 5. Comparison of planned cumulative doses and median cumulative dose received per patient of oxaliplatin and 5-FU in MOSAIC [13], NSABP C-07 [9], Nordic-FLOX [11], and in our study

	MOSAIC mg/m^2	*NSABP C-07 mg/m^2*	*Our study mg/m^2*
Planned cumulative dose of oxaliplatin	1020	765	1020
Median cumulative dose of oxaliplatin received per patient	894	676	800
Median cumulative received rate of oxaliplatin	At least 80%	At least 80%	Median 81%
Planned cumulative dose of 5-FU	24000	9000	12000
Median cumulative dose of 5-FU received per patient	21759	7003	10822

Prophylactic G-CSF was used in 19 (35.8%) patients. The reason for dose modification in 9 patients was grade II neurotoxicity, while 3 patients had dose reduction because of grade II hepatotoxicity. Grade III nausea and vomiting was the cause for dose reduction in only one patient. Comparison of toxicities between the present and other oxaliplatin-based regimen studies is shown in Table 4.

The median total oxaliplatin dose received per patient was 800 mg/m^2 (1366 mg), and the patients received a median of 81% of the planned cumulative oxaliplatin dose (Table 5).

Discussion

The addition of oxaliplatin to 5-FU-LV has clearly demonstrated a survival benefit in patients with stage III and high-risk stage II CRC. After 2 large-scale randomized trials, similar survival benefit but different toxicity rates have been defined between 2 chemotherapy regimens, FOLFOX4 (an infusional regimen) and FLOX (a bolus regimen). Nordic-FLOX is another bolus oxaliplatin-5-FU-LV combination that was studied previously in patients with advanced disease. This regimen had been evaluated as a first-line treatment in 82 metastatic CRC patients in a multicenter phase II study [11]. Grade III/IV neutropenia was reported in 26 (32%) patients, grade III thrombocytopenia in 11%, and grade III diarrhea in 7% of the patients. The incidence of grade II and III neuropathy was 41% and 13%, respectively (Table 4). However, despite higher toxicity rates, the overall response rate was 62%, and median survival 16.1 months. The high toxicity rates of Nordic-FLOX in that study were attributed to the patients' poor characteristics [11]. Because Nordic-FLOX is an effective and safe treatment in advanced disease and FLOX as a bolus regimen is effective in the adjuvant setting, we administered Nordic-FLOX as an adjuvant therapy in patients with resected stage III colon cancer and demonstrated the toxicity and efficacy of this regimen in this report.

The MOSAIC and NSABP C-07 trials are the two important randomized trials that used oxaliplatin and 5-FU-LV combination. In the MOSAIC trial 2246 patients with stage II or III colon cancer were enrolled and randomized to receive either infusional 5-FU-LV or FOLFOX4 (oxaliplatin 85 mg/m^2 d 1, LV 200 mg/m^2 d 1-2, 5-FU 400 mg/m^2 bolus d 1-2, and 600 mg/m^2 d 1-2, as 22-h infusion) every 14 days for 12 cycles. The DFS rate at 3 years was 78.2% for FOLFOX4 vs. 72.9% for 5-FU-LV in the entire patient population (p=0.002), while it was 72.2 vs. 65.3% (significant difference according to the authors) in stage III patients according to subgroup analysis [13]. After a median follow-up of 82 months, 5-year probability of DFS was significantly higher with FOLFOX4 in stage III disease (66 vs. 59%, p=0.05), while it was not significant for stage II disease (84 vs. 80%, p=0.258) [8]. In the NSABP C-07 trial, 2492 patients with stage II and III were randomly assigned to receive either FLOX (oxaliplatin 85 mg/m^2 d1 every 2 weeks, 5-FU 500 mg/m^2 bolus d1 weekly, LV 500 mg/m^2 d1 weekly for 6 weeks with a 2-week rest for 6 months) or bolus 5-FU-LV only. FLOX showed a similar DFS rate at 3 years (76.1% for FLOX vs. 71.8%

for 5-FU-LV, p=0.0034) [9]. In summary, both of these regimens showed superiority to 5-FU-LV combination only. In the present study, only stage III patients received this treatment, which is different from NSABP C-07 and MOSAIC since those studies included stage II and stage III patients. Also, another important point is that some of our patients had adverse prognostic factors like inadequate resection (the surgical resection margin was R1 in 13 patients and R2 in 2) and the follow-up time was short for some of them. Despite these negative factors, the probability of DFS at 36 months was 72% in our study which is approximately similar to FOLFOX4 regimen (Figure 1). Besides, the estimated OS at 36 months was 85% and the estimated median OS was 47.8 months (Figure 2).

Despite the similar efficacy of these randomized trials and our study, toxicity was different from each other. Grade III neutropenia in the MOSAIC trial was 41.1%. Neutropenic fever was reported in 1.8% and grade III-IV neuropathy (NCI Common toxicity criteria for adverse events scoring system/version 1) in 12.4% of the patients. In the MOSAIC trial most of the patients received at least 80% of the total oxaliplatin dose (which was equal to 1020 mg/m^2). Grade III-IV diarrhea was reported 10.8% of the patients but severe diarrhea with grade IV neutropenia with or without bacteremia was not seen in any of the patients [14]. The NSABP C-07 trial used the NCI CTCAE scoring system/version 2 which includes grade IV (permanent sensory loss), and the percentage of grade III-IV neurotoxicity was reported as 6.9%. This lower percentage in the MOSAIC study was thought to be related to the lower cumulative total dose of oxaliplatin than in FOLFOX (765 mg/m^2 in FLOX vs. 1020 mg/m^2 in FOLFOX). Grade III neutropenia was reported in 8.1% of the patients, while neutropenic fever was seen in 4.8% of the patients. The higher percentage of neutropenia in the MOSAIC study as compared to the percentage observed in NSABP C-07 study (8.1%) was thought to be due to the fact that the neutrophil nadir counts were reported for MOSAIC, whereas neutrophil counts only on the day of chemotherapy were reported for NSABP C-07. Severe diarrhea with grade IV neutropenia were more common than in FOLFOX [14]. Grade III-IV diarrhea was reported in 38% of the patients, and grade IV neutropenia and combined grade III-IV diarrhea was reported in 22 patients [9]. Although grade III-IV neutropenia and neurotoxicity was higher in FOLFOX than in FLOX, severe diarrhea was more common in FLOX. In our study Nordic-FLOX regimen was used as adjuvant chemotherapy for resected stage III colon cancer (only node positive) for 12 cycles. The cumulative planned oxaliplatin dose was the same as in FOLFOX and the patients received a median of 81% of the total cumulative dose. Although the median oxaliplatin dose received per patient was approximately the same as in FOLFOX4 (800 mg/m^2 for our study vs. 894 mg/m^2 for MOSAIC) and higher than in FLOX (676 mg/m^2 for NSABP C-07) (Table 5), grade III neurotoxicity was not seen in our study in contrast to these large randomized trials (Table 4). This may be attributed to the infusion of magnesium sulfate (1.5 g) and calcium gluconate (225 mg) which were given as an infusion before the beginning of each chemotherapy cycle. In previous studies the infusion of calcium/magnesium before oxaliplatin were associated with conflicting results about efficacy [15-17]. However, it was proven that 1 g calcium gluconate plus 1 g magnesium sulfate pre- and post-oxaliplatin were related with significantly lower rates of grade II or greater neurotoxicity in a recent randomized trial [18]. In our study Nordic-FLOX regimen was given after an infusion of calcium 225 mg and magnesium 1 g. The lower rate of peripheral neurotoxicity and the absence of grade III-IV neuropathy are probably related to the preventive effect of these cations as seen in recent studies [15,19]. However, the amount of calcium in our study was lower as compared with the other studies. The incidence of grade III neutropenia (15.1% in our study vs. 41% in MOSAIC) and grade III diarrhea (11.3% in our study vs. 38% in NSABP C-07) was also lower as compared with the previous randomized trials (Table 4). Grade IV febrile neutropenia with grade III/IV diarrhea were not seen in any of our patients in contrast to the other bolus study NSABP C-07. The cumulative planned dose of 5-FU per patient was 24000 mg/m^2 for FOLFOX4, and 9000 mg/m^2 for FLOX. In our protocol the planned dose of 5-FU was 12000 mg/m^2, and the patients received a median cumulative dose of 10822 mg/m^2 (90% of the planned dose) (Table 5). Despite the higher doses of 5-FU given in our study as compared with FLOX regimen, gastrointestinal toxicity was lower than in FLOX (Table 4). Another difference of Nordic-FLOX regimen is that the cumulative planned dose of LV was lower than in FOLFOX4 and FLOX regimens, because LV was given at 60 mg/m^2 dose for 2 days in each 2-week cycle while it was 500 mg/m^2 for 6 weeks with a 2-week rest period in FLOX regimen and 200 mg/m^2 for 2 days in every 2 weeks in FOLFOX4. Enough data from previous trials show that higher or lower doses of LV are not different in efficacy, but it had been demonstrated that lower bolus doses of LV were related with a greater gastrointestinal toxicity compared with higher doses and infusional regimens [20,21]. In the present study, although the patients received lower doses of LV compared to other regimens (FLOX and FOLFOX4), the rate of gastrointestinal toxicity -like diarrhea- was lower than expected. Only grade I and II diarrhea were

seen in our patients, severe diarrhea (grade III/IV) was not observed (Tables 3 and 4). This might be attributed to the fact that FLOX (in NSABP C-07) is a weekly-administered regimen and higher gastrointestinal toxicity may be due to 5-FU given every week. Also an explanation for the higher rate of grade III diarrhea in FOLFOX4 may be the higher cumulative dose of 5-FU compared with our regimen (Table 5).

Nordic-FLOX regimen is an effective and feasible bolus chemotherapy regimen which was previously studied in patients with metastatic CRC. No central venous catheter or infusion pump is required for this therapy and this is comfortable for the patients. Complications due to the procedure itself such as thrombosis or infection are not seen. Therefore, due to its lower toxicity and similar efficacy it can be used as an adjuvant treatment at least in patients for whom pump infusion is not feasible or available. However, a study with larger patient number and longer follow-up time is required to prove the similar efficacy of this regimen compared with FOLFOX4 in the adjuvant setting.

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