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Retrospective analysis of the effect of CAPOX and mFOLFOX6 dose intensity on survival in colorectal patients in the adjuvant setting

A. Mamo PhD,* J. Easaw MD,† F. Ibnshamsah MD,† A. Baig MD,* Y.S. Rho MD,* T. Kavan BSc,* G. Batist MD,* and P. Kavan MD PhD*

ABSTRACT

Background Despite lack of a true comparative study, the FOLFOX (5-fluorouracil–leucovorin–oxaliplatin) and CAPOX (capecitabine–oxaliplatin) regimens are believed to be similar in their efficacy and tolerability in the treatment of stage III colorectal cancer. However, that belief has been disputed, because real-life data suggest that the CAPOX regimen is more toxic, leading to more frequent reductions in the delivered dose intensity—thus raising questions about the effect of dose intensity on clinical outcomes.

Methods A retrospective data review for two Canadian institutions, the Segal Cancer Centre and the Tom Baker Cancer Centre, considered patients diagnosed with stage III colorectal cancer during 2006–2013. Primary endpoints were dose intensity and toxicity, with a secondary endpoint of disease-free survival.

Results The study enrolled 180 eligible patients (80 at the Segal Cancer Centre, 100 at the Tom Baker Cancer Centre). Of those 180 patients, 75 received CAPOX, and 105 received mFOLFOX6. In the CAPOX group, a significant dose reduction was identified for capecitabine compared with 5-fluorouracil in mFOLFOX6 group ($p = 0.0014$). Similarly, a significant dose reduction was observed for oxaliplatin in mFOLFOX6 compared with oxaliplatin in CAPOX ($p = 0.0001$). Compared with the patients receiving CAPOX, those receiving mFOLFOX6 were twice as likely to experience a treatment delay of more than 1 cycle-length ($p = 0.03855$). Toxicity was more frequent in patients receiving mFOLFOX6 (nausea: 30% vs. 18%; diarrhea: 47% vs. 24%; peripheral sensory neuropathy: 32% vs. 3%). At a median follow-up of 40 months, preliminary data showed no difference in disease-free survival ($p = 0.598$). Pooled data from both institutions were also separately analyzed, and no significant differences were found.

Conclusions Our results support the use of CAPOX despite a lack of head-to-head randomized trial data.

Key Words CAPOX, mFOLFOX6, dose intensity, disease-free survival, colorectal cancer

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INTRODUCTION

Fluoropyrimidines—and in particular 5-fluorouracil (5FU)—have largely been the backbone of chemotherapy for colon cancer in the adjuvant setting[1]. Randomized clinical trials have consistently shown that, compared with 5FU and leucovorin (LV) alone, the addition of oxaliplatin (FOLFOX) results in superior response rates and time to disease progression, as exemplified by the North Central Cancer Treatment Group trial N9741 and the MOSAIC studies in stage III patients[2,3].

Recently, complications related to central venous catheters for 5FU–LV arose in both the hospital and community settings. The substitution of infusional or bolus 5FU with oral capecitabine has been an active area of research since the early 2000s. In the adjuvant setting, almost all studies comparing capecitabine monotherapy with bolus 5FU–LV regimens resulted in

Correspondence to: Petr Kavan, 3755 Cote-Ste Catherine, Montreal, Quebec H3T 1E2.
E-mail: petr.kavan@mcgill.ca **DOI:** http://dx.doi.org/10.3747/co.23.3059

a similar response rate, disease-free progression, and overall survival (OS)[4,5]. Consensus on the toxicity profiles of the capecitabine arms compared with the 5FU–LV infusion arms has been somewhat variable, but in general, grade 3 occurrences of diarrhea, hand–foot syndrome, and thrombocytopenia have been significantly higher with the CAPOX regimens, and grade 3 neutropenia and febrile neutropenia seem to occur significantly more often with the FOLFOX regimens[6].

Loree *et al.* demonstrated that, compared with the mFOLFOX6 regimen, treatment with CAPOX was associated with a lower relative dose intensity (RDI) and higher-grade toxicities. However, those characteristics did not seem to affect clinical outcomes, which were observed to be better in patients receiving CAPOX despite the lower doses of chemotherapy[7]. The foregoing results suggested that the incidence of capecitabine-associated dose-limiting toxicities is higher in clinical practice than was reported in trials, leading to a reduction in the RDI for capecitabine. Recently, Ho *et al.*[8] reported a retrospective study to examine the pattern and effects of dose-limiting toxicities and RDI on relapse-free survival and OS in patients receiving adjuvant capecitabine for colorectal cancer. They concluded that, in clinical practice, dose-limiting toxicities from adjuvant capecitabine monotherapy are not uncommon and can lead to a reduced RDI. However, achieving a RDI of more than 70% was independently associated with relapse-free survival and OS[8]. Moreover, Romano and colleagues analyzed retrospective data from patients treated in the adjuvant setting with mFOLFOX6 and CAPOX to identify how frequently chemotherapy was prematurely discontinued for toxicity in routine clinical practice. They showed that, because of toxicity, the planned dose of oxaliplatin was administered in 11% of patients receiving CAPOX and in 80% of those receiving mFOLFOX6 ($p < 0.005$) in a non-clinical-trial population. That observation suggested a need to optimize toxicity management while monitoring dose intensity for patients treated with capecitabine (Romano B. Personal communication).

In the present retrospective study, we used a real-life experience to describe and review dose intensity and toxicity—and their effect on clinical outcomes—in patients treated with either mFOLFOX6 or CAPOX in adjuvant setting in two different institutional practices.

METHODS

Patient Population

At the Segal Cancer Centre [SCC-JGH (part of Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC)], 80 patients with stage III colorectal cancer were treated with either the CAPOX ($n = 37$) or the mFOLFOX6 ($n = 43$) regimen. At the Tom Baker Cancer Centre [TBCC (Calgary, AB)], 100 patients with stage III colorectal cancer were treated with either the CAPOX ($n = 38$) or the mFOLFOX6 ($n = 62$) regimen. Treatment with CAPOX or mFOLFOX6 was defined as receipt of at least 1 infusion. At both institutions, the reference CAPOX regimen was based on 8 cycles of oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 twice daily. The reference mFOLFOX6 regimen was based on 12 cycles of oxaliplatin 85 mg/m^2, 5FU 400 mg/m^2 bolus, and then 5FU 2400 mg/m^2 infused over a period of 46 hours (with leucovorin).

Available patient data were collected from the time of initial diagnosis to the time of chart review. Those data included relevant medical history (chronic diarrhea, liver dysfunction, renal failure, respiratory disease, cardiovascular disease); disease stage and tumour pathology at diagnosis; details of the chemotherapeutic regimen, duration of therapy, and line of therapy; and details of primary surgery.

The primary endpoints for both settings were dose intensity with safety analysis. The secondary endpoint was efficacy in terms of disease-free survival (DFS)—that is, the length of time from initiation of treatment till recurrence. Patients underwent computed tomography imaging every 3–6 months, per standard clinical guidelines for tumour assessments. The grading of toxicities was based on safety guidelines per the *Common Terminology Criteria for Adverse Events,* version 4.0. The Kaplan–Meir method was used to analyze survival data[9].

Statistical Methods

"Dose reduction" was defined as a more than 10% decrease from the standard prescribed dose. The reductions were defined and analyzed in different two ways:

- *A priori* dose reductions that occurred before treatment initiation at cycle 1
- Subsequent dose reductions that occurred after initiation of treatment

Treatment delays were identified when the actual treatment period (based on the treatment start date and the calculated last day of the final cycle, based on the date of the final dose) exceeded the calculated treatment period (number of cycles multiplied by the number of weeks in a standard cycle) by at least 1 cycle-length (CAPOX: 3 weeks; mFOLFOX6: 2 weeks).

In addition, to explore the number of patients who actually received the full amount of prescribed treatment without dose modification or delay in the adjuvant setting, actual treatment received was compared with the standard expected treatment (that is, 8 cycles of CAPOX or 12 cycles of mFOLFOX6).

Dose intensity and RDI were calculated using methods previously described. This equation was used for dose intensity:

$$\text{Dose intensity} = \text{total drug given (mg/m}^2\text{)} \,/\, \text{total treatment time (weeks)}$$

For the analysis of RDI in the adjuvant setting, independent t-tests and Fisher exact tests were used.

RESULTS

Patient Characteristics

As shown in Table I, 80 stage III patients received adjuvant treatment at the SCC-JGH, with 37 receiving at least 1 infusion of CAPOX and 43 receiving at least 1 infusion of mFOLFOX6. Median age in the CAPOX group was 65 years

TABLE I Baseline patient characteristics

Characteristic	Treatment setting and regimen			
	Segal Cancer Centre		Tom Baker Cancer Centre	
	CAPOX	mFOLFOX6	CAPOX	mFOLFOX6
Patients (*n*)	37	43	38	62
Age at diagnosis (years)				
Median	65	66	59	58
Range	18–82	33–80	23–82	24–81
Primary site [*n* (%)]				
Colon only	28 (75)	24 (56)	38 (100)	62 (100)
Rectum only	9 (23)	19 (40)	0	0
Stage at diagnosis [*n* (%)]				
III	37 (100)	43 (100)	38 (100)	62 (100)
ECOG PS at chemotherapy start [*n* (%)]				
0	20 (55)	32 (80)	21 (55)	34 (55)
1	16 (43)	7 (17)	17 (45)	28 (45)
2	0	1 (3)	0	0
Unknown	1 (2)	3 (7)	0	0

CAPOX = capecitabine–oxaliplatin; mFOLFOX6 = oxaliplatin–leucovorin–5-fluorouracil; ECOG = Eastern Cooperative Oncology Group; PS = performance status.

(range: 18–82 years); in the mFOLFOX6 group, it was 66 years (range: 33–80 years). Of the 37 patients receiving CAPOX, 28 (76%) were diagnosed with colon cancer, and 9 (24%), with rectal cancer. Of the 43 patients receiving mFOLFOX6, 24 (56%) had colon cancer, and 19 (44%) had rectal cancer. Eastern Cooperative Oncology Group (ECOG) performance status varied between 0 and 1, with 31 of the CAPOX patients (84%) being assessed as ECOG 0, and 6 (16%) as ECOG 1; and 32 of the mFOLFOX6 patients (74%) being assessed as ECOG 0, and 11 (26%) as ECOG 1.

At the TBCC, 100 stage III patients received treatment with either CAPOX ($n = 38$) or mFOLFOX6 ($n = 62$). Median age in the CAPOX group was 59 years; in the mFOLFOX6 group, it was 58 years. All patients, whether receiving CAPOX or mFOLFOX6, had been diagnosed with colon cancer. Performance status varied between 0 and 1, with 21 of the CAPOX patients (55%) being assessed as ECOG 0, and 17 (45%) as ECOG 1; and 34 of the mFOLFOX6 patients (55%) being assessed as ECOG 0, and 28 (45%) as ECOG 1.

Delivered Chemotherapy RDI

At the SCC-JGH, oxaliplatin in the CAPOX regimen was found to delivered at a mean actual dose intensity of 31.2 mg/m^2 weekly (range: 12.4–43.3 mg/m^2), for a 28% upfront reduction from the theoretical standard dose intensity of 43.3 mg/m^2 weekly (Table II). Capecitabine in the CAPOX regimen was found to be delivered at a mean actual dose intensity of 6957 mg/m^2 weekly (range: 1881–9699 mg/m^2), for a 25% upfront reduction from the theoretical standard dose intensity of 9333 mg/m^2 weekly. In contrast, oxaliplatin in the mFOLFOX6 regimen was found to be delivered at a mean actual dose intensity of 36.3 mg/m^2 weekly (range: 7.9–45.6 mg/m^2), for a 15% upfront reduction from the theoretical standard dose intensity of 42.5 mg/m^2 weekly. The 5FU in the mFOLFOX6 regimen was found to be delivered at a mean actual dose intensity of 1203 mg/m^2 weekly, for a 14% upfront reduction from the theoretical standard dose intensity of 1400 mg/m^2 weekly.

At the TBCC, oxaliplatin in the CAPOX regimen was found to be delivered at a mean actual dose intensity of 32.1 mg/m^2 weekly (range: 13.0–43.0 mg/m^2), for a 22% upfront reduction from the theoretical standard dose intensity of 43.3 mg/m^2 weekly (Table II). Capecitabine in the CAPOX regimen was found to be delivered at a mean actual dose intensity of 7280 mg/m^2 weekly (range: 1900–9800 mg/m^2), for a 22% upfront reduction from the theoretical standard dose intensity of 9333 mg/m^2 weekly. Oxaliplatin in the mFOLFOX6 regimen was found to be delivered at a mean actual dose intensity of 37.5 mg/m^2 weekly (range: 12.5–46.0 mg/m^2), for a 14% upfront reduction from the theoretical standard dose intensity of 43.5 mg/m^2 weekly. The 5FU in the mFOLFOX6 regimen was found to be delivered at a mean actual dose intensity of 1260 mg/m^2 weekly (range: 270–1470 mg/m^2), for a 10% upfront reduction from the theoretical standard dose intensity of 1400 mg/m^2 weekly.

Comparison by t-test analysis of the dose intensities of oxaliplatin and of capecitabine or 5FU in CAPOX and mFOLFOX6 resulted in $p = 0.0001$ for oxaliplatin and $p = 0.0014$ for capecitabine or 5FU, suggesting that, in the adjuvant setting, significant dose reductions in oxaliplatin and capecitabine occurred in the CAPOX regimen compared with the mFOLFOX6 regimen.

TABLE II Dose intensity (DI) analysis

Dose intensity variable	Treatment setting and regimen			
	Segal Cancer Centre		Tom Baker Cancer Centre	
	CAPOX (*n*=37)	mFOLFOX6 (*n*=43)	CAPOX (*n*=38)	mFOLFOX6 (*n*=62)
Oxaliplatin DI (mg/m^2 weekly)	43.3		41.3	
Theoretical standard	31.2	42.5	32.1	43.5
Actual				
Mean		36.3		37.5
Range	12.4–43.3	7.9–45.6	13.0–43.0	12.5–46.0
Relative				
Mean	0.72	0.85	0.78	0.86
Range	0.29–1.00	0.2–1.1	0.3–1.1	0.25–1.2
Capecitabine DI (mg/m^2 weekly)				
Theoretical standard	9333		9333	
Actual				
Mean	6957		7280	
Range	1881–9699		1900–9800	
Relative				
Mean	0.75		0.78	
Range	0.20–1.04		0.25–1.1	
Actual:standard ratio[a]				
Mean	0.67			
Range	0.10–1.00			
5-Fluorouracil DI (mg/m^2 weekly)				
Theoretical standard		1400		1400
Actual				
Mean		1203		1260
Range		261–1439		270–1470
Relative				
Mean		0.86		0.90
Range		0.2–1.0		0.2–1.1

[a] Nonmetastatic patients only.
CAPOX = capecitabine–oxaliplatin; mFOLFOX6 = oxaliplatin–leucovorin–5-fluorouracil.

Safety, Treatment Duration, and Delays

At the SCC-JGH, the median number of completed CAPOX cycles was 8 (range: 1–10 cycles); for MFOLFOX6, 10 cycles were completed (range: 1–18 cycles; Table III). Of patients receiving CAPOX, 39% did not complete the standard 8 cycles; of patients receiving MFOLFOX6, 53% did not complete the standard 12 cycles. At the TBCC, the median number of completed CAPOX cycles was 8 (range: 1–10 cycles); for MFOLFOX6, 10 cycles were completed (range: 1–18 cycles). Of patients receiving CAPOX, 26% did not complete the standard 8 cycles; of patients receiving MFOLFOX6, 42% did not complete the standard 12 cycles.

In fact, as Table IV shows, 40% of the patients receiving the MFOLFOX6 regimen (17 of 43 at the SCC-JGH and 25 of 62 at the TBCC) experienced treatment delays of more than 1 cycle-length, whereas 20% of those receiving the CAPOX regimen (7 of 37 at the SCC-JGH and 8 of 38 at the TBCC) experienced such delays. The identified delays were associated with a higher proportion of certain adverse events being experienced by the patients receiving MFOLFOX6 than by the patients receiving CAPOX (nausea: 30% vs. 18% respectively; diarrhea: 47% vs. 24%; peripheral sensory neuropathy: 32% vs. 3%).

Survival Analysis

After a median follow-up of 40 months, preliminary data showed no DFS differences between the regimens (p = 0.598). More than 90% of patients treated with either CAPOX

TABLE III Treatment duration and delays

Variable	Treatment setting and regimen			
	Segal Cancer Centre		Tom Baker Cancer Centre	
	CAPOX (*n*=37)	mFOLFOX6 (*n*=43)	CAPOX (*n*=38)	mFOLFOX6 (*n*=62)
Patients[a] [*n* (%)] completing fewer than the standard number of cycles (8 or 12)	14 (39)	23 (53)	10 (26)	26(42)
Cycles completed (*n*)				
Median	8	10	8	10
Range	1–10	1–18	1–10	1–18
Treatment delays >1 cycle-length [*n* (%) patients]	7 (20)	117 (40)	8 (20)	25 (40)

[a] Nonmetastatic patients only.
CAPOX = capecitabine–oxaliplatin; mFOLFOX6 = oxaliplatin–leucovorin–5-fluorouracil.

TABLE IV Toxicities leading to dose modification after treatment cycle 1 in nonmetastatic patients

Regimen	Toxicity													
	Infusion reaction	Nausea	vomiting	Diarrhea	Neutropenia	Febrile neutropenia	Thrombocytopenia	Paresthesia	Anorexia	Hand–foot syndrome	Constipation	Abdominal pain	Pyrexia	Peripheral sensory neuropathy (at least grade 2)
CAPOX	0	18	17	24	0	0	3	1	0	1	0	4	2	3
mFOLFOX6	0	30	15	47	33	0	30	18	4	0	2	0	0	32

CAPOX = capecitabine–oxaliplatin; mFOLFOX6 = oxaliplatin–leucovorin–5-fluorouracil.

or mFOLFOX6 were still alive. Pooled data from both institutions were also separately analyzed, and no significant differences were found (Figure 1).

DISCUSSION

Our report evaluated the dose intensity and safety of the CAPOX and mFOLFOX6 regimens in the adjuvant setting and showed that, in real-life practice, dose reductions in the CAPOX regimen did not seem to affect clinical outcomes.

Our retrospective analysis examined real-world patients treated at two different Canadian institutions and showed higher upfront dose reductions with the CAPOX regimen than with the mFOLFOX6 regimen. We also observed a greater proportion of patients with nausea, diarrhea, and neuropathy in the mFOLFOX6-treated group than in the CAPOX-treated group. Those adverse events led to treatment delays in 50% of patients treated with mFOLFOX6, but in only 20% of those receiving CAPOX.

Our results accord with the single-institution report by Loree *et al.*[7], who showed that patients prescribed CAPOX received lower doses of oxaliplatin and capecitabine. A number of trials have shown that, although the full dose of both agents was recommended for the treatment of patients with advanced colorectal cancer, more than 25% of the chemotherapy-naïve population required a capecitabine dose reduction after cycle 1[10–13].

Next, we wanted to verify whether dose reductions could affect clinical outcomes such as DFS. The preliminary results from both institutions showed no survival disadvantage for CAPOX compared with mFOLFOX6 (Figure 1). Interestingly, results by Loree *et al.*[7] showed that survival analyses demonstrated a trend toward improved OS with CAPOX [hazard ratio (HR): 0.4741; 95% confidence interval (CI): 0.1660 to 1.354; $p = 0.1663$] and an improved DFS with CAPOX (HR: 0.4949; 95% CI: 0.2512 to 0.9749; $p = 0.0420$). Multivariate analyses demonstrated similar results, with CAPOX being associated with a trend toward improved OS (HR: 0.396; 95% CI: 0.110 to 1.429) and DFS (HR: 0.458; 95% CI: 0.210 to 1.001; $p = 0.0504$). Moreover, the X-ACT trial, a multicentre randomized trial, demonstrated the noninferiority of capecitabine compared with intravenous 5FU–LV[4,14,15]. Although that trial had been designed only as a noninferiority trial, it nevertheless demonstrated

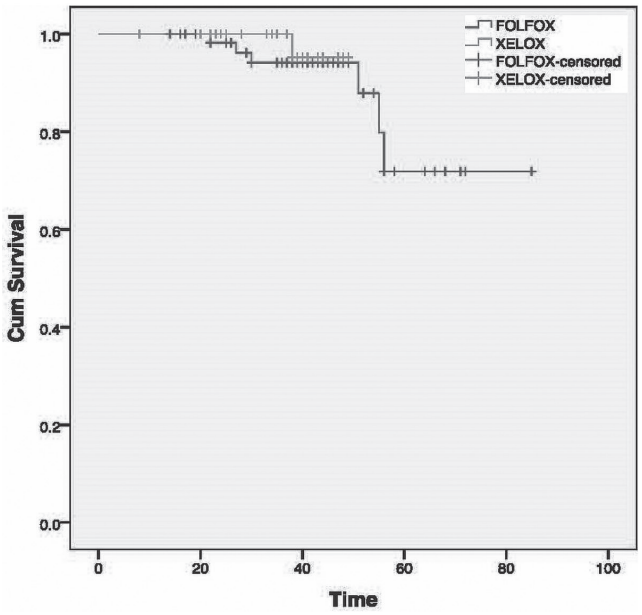

FIGURE 1 Clinical outcomes in patients treated with CAPOX (capecitabine–oxaliplatin) or mFOLFOX6 (oxaliplatin–leucovorin–5-fluorouracil).

trends toward improved DFS and OS with capecitabine. If capecitabine is noninferior to 5FU–LV, that noninferiority might therefore also be observed for regimens adding oxaliplatin to those agents.

Alternatively, the difference in outcomes might be explained by factors such as patient selection and time to initiation of adjuvant chemotherapy. Our data from both participating institutions showed no difference between CAPOX and mFOLFOX6 for time to initiation of adjuvant therapy, suggesting that any delay potentially associated with central line placement was not a contributor to clinical outcomes. Another possible explanation is that the intended oxaliplatin dose intensity used in CAPOX is larger than the intended oxaliplatin dose intensity used in mFOLFOX6. The target oxaliplatin dose is 130 mg/m^2 every 3 weeks in CAPOX and 85 mg/m^2 every 2 weeks in mFOLFOX6. Although the total dose of oxaliplatin over the adjuvant period is intended to be very similar in both regimens, the larger dose density with each cycle of CAPOX might help to explain why more dose-limiting toxicities were observed with CAPOX and might also suggest more activity against residual tumour cells in the adjuvant setting.

Overall, our results demonstrate that treatment with a lower dose of CAPOX does not seem to affect clinical outcomes, which were observed to be better in patients receiving CAPOX. We acknowledge that these results have to be confirmed in larger studies. However, they are important in assessing the comparison of CAPOX and FOLFOX in the adjuvant setting, because lower doses of CAPOX would result in lower incremental costs, which has important implications for oncology expenditures and institutional budgets.

CONCLUSIONS

We describe a real-life experience of patients treated with either mFOLFOX6 or CAPOX in the adjuvant setting at two different institutions, reviewing dose intensity and toxicities and their effect on patient outcomes. Our report shows that, in real-life practice, dose reductions in the CAPOX regimen do not seem to affect clinical outcomes. These similar results, which were obtained at two different large centres, also suggest uniform practice in gastrointestinal oncology across Canada.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

*Department of Oncology, McGill University, and the Segal Cancer Centre, Sir Mortimer B. Davis Jewish General Hospital, Montreal, QC; †Tom Baker Cancer Centre, Calgary, AB.

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