

Capecitabine Plus Oxaliplatin vs Infusional 5-Fluorouracil Plus Oxaliplatin in the Treatment of Colorectal Cancer

The CapeOx Regimen is Preferred Over FOLFOX

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Chemotherapy for the treatment of colorectal cancer has undergone a significant evolution during the past decade. Until a few years ago, the only chemotherapy for colorectal cancer was intravenous (IV) 5-fluorouracil (5-FU) in combination with the biochemical modulator leucovorin (LV) in various dosing schedules (eg, the Mayo Clinic, Roswell Park, de Gramont, and Lokich regimens).¹ Recently, 2 new agents, irinotecan (Camptosar, Pfizer) and oxaliplatin (Eloxatin, Sanofi-Aventis), have emerged as essential components of systemic chemotherapy for colorectal cancer along with 5-FU. The availability of these 3 agents improves the survival of patients with advanced colorectal cancer.² Oxaliplatin, in combination with infusional 5-FU/LV (the FOLFOX regimen) has proved more effective than 5-FU/LV therapy alone as both first-line^{3,4} and second-line⁵ therapy for metastatic colorectal cancer. Recently, a large intergroup trial (N9741) showed significant improvements in response rate, time to disease progression, and overall survival with FOLFOX versus irinotecan plus bolus 5-FU/LV (ILF).⁶ Today, either FOLFOX or FOLFIRI (infusional 5-FU/LV with irinotecan), now with the addition of the monoclonal antibody bevacizumab, has become the standard first-line treatment for advanced colorectal cancer.⁷ The

Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) also established the role of FOLFOX in adjuvant therapy for stage II and III colorectal cancer.⁸

Although the prolonged infusion of 5-FU in combination with oxaliplatin (FOLFOX) and irinotecan (FOLFIRI) has improved safety and efficacy, the inconvenience and morbidity associated with long-term central venous access emphasizes the need for alternative regimens. One of the most promising such approaches involves substituting capecitabine (Xeloda, Roche) for IV 5-FU.

Capecitabine as a Single Agent in the Management of Colorectal Cancer

Capecitabine is an oral fluoropyrimidine that was rationally designed to be converted to active 5-FU preferentially in tumor tissues.⁹ Therefore, it might have greater efficacy as a result of delivering high levels of 5-FU selectively in tumors. Early phase I and phase II studies showed that an intermittent schedule of capecitabine alone at 1,250 mg/m² twice daily was a preferred regimen.^{10,11} Subsequently, 2 large phase III trials were conducted, one in the United States¹² and the other in Europe,¹³ to compare capecitabine (at 1,250 mg/m² twice daily for 14 days followed by 7 days of rest) with the conventional Mayo Clinic schedule of 5-FU/LV (5-FU 425 mg/m²/day and low-dose LV 20 mg/m²/day for 5 days). The pooled analysis of 603 capecitabine-treated patients and 604 5-FU/LV-treated patients from these 2 randomized trials showed that the clinical response rate was significantly better in the capecitabine group than in the 5-FU/LV group.¹⁴ The median time to disease progression, overall survival, and duration of response were equivalent in the 2 treatment groups. The toxicity profile seemed to be better in the capecitabine-treated group when all grades of clinical toxicities were considered, including diarrhea, stomatitis, nausea, alopecia, leucopenia, and neutropenia. The capecitabine-treated group had more hand-foot-syndrome. These encouraging results led to the approval

of capecitabine as a first-line treatment for advanced colorectal cancer in the United States and worldwide.

The X-ACT trial (Xeloda in Adjuvant Colon Cancer Therapy),¹⁵ a large phase III trial involving 1,987 patients, also showed that oral capecitabine (1,250 mg/m² twice a day) is as effective as bolus 5-FU/LV (the Mayo Clinic regimen) when given as adjuvant therapy after complete resection of stage III colon cancer and is associated with a better toxicity profile.

In summary, single-agent capecitabine offers an efficacy as good as or better than the bolus 5-FU/LV regimens, as both first-line and adjuvant treatment for colorectal cancer, and it has a better toxicity profile.

Capecitabine in Combination with Oxaliplatin in the Management of Colorectal Cancer

It is logical to combine capecitabine with oxaliplatin (CapeOx) in the treatment of colorectal cancer for several reasons: (1) capecitabine has efficacy similar to or better than that of bolus 5-FU/LV with a better toxicity profile; (2) infusional 5-FU is superior to bolus 5-FU and has both better efficacy and a better toxicity profile, and capecitabine mimics infusional 5-FU; and (3) oxaliplatin is synergistic with 5-FU, and the FOLFOX regimen has become one of the standard treatments for colorectal cancer both in advanced disease and in adjuvant settings. In addition, preclinical studies have indicated oxaliplatin upregulates thymidine phosphorylase, the key enzyme involved in tumor-specific generation of 5-FU from capecitabine in human colon cancer tumor tissues, thereby inducing supra-additive activity with CapeOx that may not occur with FOLFOX.¹⁵

Early phase I studies explored various doses and schedules of capecitabine and oxaliplatin.¹⁶⁻¹⁸ In those studies, diarrhea was usually the dose-limiting toxicity. Since then, at least 8 phase II trials have been conducted using the CapeOx combination as the first-line treatment for colorectal cancer (Table 1). The most common regimen uses oral capecitabine at 1,000–1,250 mg/m² twice daily on days 1–14 with oxaliplatin at 120–130 mg/m² on day 1, repeated every 3 weeks. In the largest phase II trial using this regimen, 96 patients with metastatic colorectal cancer received first-line CapeOx in a 3-week treatment cycle, using IV oxaliplatin at 130 mg/m² on day 1 followed by oral capecitabine at 1,000 mg/m² twice daily for 2 weeks.¹⁵ A total of 53 of the 96 patients (55%) achieved an objective response, and 30 (31%) experienced disease stabilization for at least 3 months after treatment, for a total clinical benefit rate of 86% (Table 2). The median time to disease progression was 7.7 months, and the median overall survival was 19.5 months. These efficacy

results compared favorably with those from randomized studies of the FOLFOX regimen. CapeOx achieved response rates and progression-free and overall survival similar to those of the regimens combining protracted 5-FU/LV infusion with oxaliplatin. Capecitabine and oxaliplatin do not have overlapping toxicities. The safety profile of CapeOx was similar to that of FOLFOX but with less myelosuppression.

Three smaller phase II studies using the same regimen showed response rates of 31–42.2%.¹⁹⁻²¹ Of note, in contrast to the generally low toxicities in the European studies,^{15,19,20} the US study using the same CapeOx regimen showed significant toxicity that required a 25% reduction in the dose of capecitabine.²¹ The reasons for the discrepancy between the European and American experiences were unclear. The postulated hypotheses include (1) differences in perceptions and recording of side effects, (2) potential adverse effects of commonly used vitamin supplements, and (3) pharmacogenomic variations. Given the limited number of patients involved in these trials, it is also possible that the reported toxicity rates may have overlapping 95% confidence intervals (CIs). Detailed analyses of the toxicity patterns in ongoing and future phase III trials will help clarify this issue.

Before completion of the dose-escalation study,¹⁷ 2 studies using a similar schedule but a higher dosage of capecitabine were initiated.^{20,22} One used a 3-week cycle of capecitabine at 1,250 mg/m² twice daily on days 1–14 with oxaliplatin at 130 mg/m² on day 1. The other used the same capecitabine dosage and a slightly lower dose of oxaliplatin, 120 mg/m². In these 2 studies, response rates of 49% and 48.7%, respectively, were reported for first-line therapy. However, incidences of significant grade 3/4 diarrhea were noted (38% and 28%).

Another variation of the regimen was also studied, using oxaliplatin at 70 mg/m² on days 1 and 8 with capecitabine at 1,000 mg/m² twice daily on days 1–14 in a 21-day cycle as first-line treatment for colorectal cancer.²³ An interim analysis of 77 patients was reported at the 2003 Annual Meeting of the American Society of Clinical Oncology. A response rate of 50.7% was noted, with 39% having stable disease. The progression-free survival was 7.2 months, and overall survival was more than 17 months. The diarrhea rate was 13.4%.

Early clinical evidence indicated that dose intensification of the oral 5-FU prodrug is likely to result in enhanced antitumor activity.^{11,24,25} To confirm the improved therapeutic results of the dose intensification of capecitabine, Scheithauer et al²⁶ carried out a randomized phase II trial of 2 schedules of capecitabine plus oxaliplatin as first-line treatment for advanced colorectal cancer. A total of 89 patients with previously untreated metastatic colorectal cancer were randomly assigned to

Table 1. Selective Phase II Trials of Capecitabine Plus Oxaliplatin as First-line Treatment for Colorectal Cancer

Study	Pts, N	Regimen	Clinical Activity				Toxicity (grade 3 or 4), %						Remarks
			RR, %	SD, %	PFS, mo	OS, mo	D	N/V	HFS	Neur	NTP	Thr	
Borner et al, 2002 ²²	43	OX 130 mg/m ² d1, CAP 1,250 mg/m ² BID d1–14, q21d	49	-	-	17.1	38	10	-	16	-	-	Also included 26 patients receiving second-line therapy
Grothey et al, 2003 ²³	82	OX 70 mg/m ² d1,8 CAP 1,000 mg/m ² BID d1–14, q21d	50.7	39	7.2	>17	13.4	-	2.4	7.3	-	3.8	Interim analysis of 77 patients
Carreca et al, 2003 ²⁸	33	OX 85–100 mg/m ² d1, CAP 1,000–1,250 mg/m ² BID d2–15, q21d. Individual dose escalations after cycle 1	43	-	-	-	5	-	-	-	-	-	Interim analysis of 21 patients; 70–81 yrs old
Makatsoris et al, 2003 ¹⁹	50	OX 130 mg/m ² d1, CAP 1,000 mg/m ² BID d1–14, q21d	31	-	-	-	4	4	-	-	6	2	Interim analysis of 36 patients
Scheithauer et al, 2003 ²⁶	89	Arm A (n=45): OX 130 mg/m ² d1, CAP 1,000 mg/m ² BID d1–14, q21d	42.2	-	6	-	9	11	-	16	15	4	Two-arm randomized trial with different schedules. RR btwn 2 arms significantly different (P=.0013)
		Arm B (n=44): OX 85 mg/m ² d1,14, CAP 1,750 mg/m ² BID, d1–7, 14–21, q21d	54.5	-	10.5	-	12	5	2	-	7	7	
Zeuli et al, 2003 ²⁰	43	OX 120 mg/m ² d1,14, CAP 1,250 mg/m ² BID d1–14, q21d	48.7	25.6	8.2	20	28	5	2	7	-	-	
Shields et al, 2004 ²¹	48	OX 130 mg/m ² d1, CAP 1,000 mg/m ² (reduced to 750 mg/m ² due to toxicity) BID d1–14, q21d	38.5 (37.1)	-	6.9	-	17.1	-	-	-	5.7	-	CAP dose reduced to 750 mg/m ² twice daily
Cassidy et al, 2004 ¹⁵	96	OX 130 mg/m ² d1, CAP 1,000 mg/m ² bid d1–14, q21d	55	30	7.7	19.5	16	13	3	17	7	4	Pts >65 yrs had similar favorable toxicity profile except more common stomatitis

CAP = capecitabine; D = diarrhea; HFS = hand-foot syndrome; Neur = neurological; NTP = neutropenia; N/V = nausea/vomiting; OS = overall survival; OX = oxaliplatin; PFS = progression-free survival; RR = response rate; SD = stable disease; Thr = thrombocytopenia.

Table 2. Efficacy Outcome and Grade 3/4 Toxicity of XELOX and FOLFOX from Two Selected Studies

Toxicity	Grade 3 or 4 Adverse Events, %	
	FOLFOX (N= 210)*	XELOX (N = 96)†
Neurosensory toxicity	18	17
Diarrhea	12	16
Nausea/vomiting	6	13
Hand-foot syndrome	0	3
Neutropenia	42	7
Thrombocytopenia	2.5	4
	Clinical Activity	
	FOLFOX (N= 210)*	XELOX (N = 96)†
Response rate, %	50	55
Stable disease, %	-	31
Median time to progression, mo	8.2	7.7
Median overall survival, mo	16.2	19.5

* Data from de Gramont et al.³

† Data from the largest phase II study by Cassidy et al.¹⁵

receive oxaliplatin 130 mg/m² on day 1 plus capecitabine 2,000 mg/m² on days 1–14 every 3 weeks (the conventional regimen) or oxaliplatin at 85 mg/m² on days 1 and 14 combined with capecitabine at 3,500 mg/m² on days 1–7 and 14–21 every 4 weeks (the dose-intensification regimen). Using this dose-intensification regimen, a dose of capecitabine that is 105–131.25% higher than conventional capecitabine schedules can be administered. This shorter, intermittent treatment duration of capecitabine also more closely resembles the FOLFOX regimen. The results revealed that patients on the dose-intensification schedule of capecitabine had a higher radiologically confirmed response rate and a significantly longer median progression-free survival than those on the conventional capecitabine schedule. More encouraging, despite a 34% higher dose of capecitabine, there was no difference in either hematologic or nonhematologic toxicity between the 2 treatment arms. Obviously, the superiority of the dose-intensification schedule of capecitabine needs to be confirmed by large phase III trials. Nevertheless, the comparable toxicity profile showed that the dose intensified combination of capecitabine and oxaliplatin is feasible.

As a second-line treatment for metastatic colorectal cancer, CapeOx also showed significant activity. In the study reported by Borner et al,²² 26 patients who had previously received 1 fluoropyrimidine-containing regimen for advanced colorectal cancer were treated with CapeOx on a 3-week cycle of capecitabine at 1,250 mg/m² twice daily on days 1–14 with oxaliplatin at 130 mg/m² on day 1. An objective response rate of 15% (95% CI, 4–35%) was reported, which compares favorably with the response rate of 15% (95% CI, 7–23%) when the FOLFOX regimen was administered as second-line therapy.²⁷

In summary, CapeOx with capecitabine at 1,000 mg/m² twice daily on days 1–14 in combination with oxaliplatin at 120–130 mg/m² on day 1 achieves an efficacy similar to that of FOLFOX while maintaining a good safety profile in the treatment of advanced colorectal cancer. The finding that the dose-intensification schedule of capecitabine in the CapeOx regimen seemed to be superior to the conventional dosing of capecitabine is intriguing and warrants studies directly comparing it with FOLFOX.

CapeOx Is More Convenient than FOLFOX

The CapeOx regimen requires only 1 clinic visit per 3-week cycle for a 2-hour infusion of oxaliplatin; the FOLFOX regimen requires either two 22-hour infusions of 5-FU over 3 days every 2 weeks³ or 1 46-hour infusion of 5-FU every 2 weeks, depending on the schedule used, in addition to the oxaliplatin infusions. For patients with metastatic colorectal cancer for whom the treatment is mainly palliative, these protracted infusions and clinic visits consume a considerable portion of their remaining lifetime. The requirement of a pump for FOLFOX administration also adds additional cost, patient anxiety, and inconvenience to patients. The simplified CapeOx regimen is less disruptive to patients' daily life, an aspect that is likely to have important implications for their quality of life and autonomy.

Summary

In summary, in comparison with FOLFOX, CapeOx has similar clinical efficacy, has a better toxicity profile, particularly with regard to grade 3/4 neutropenia, and is more convenient and less disruptive to patients' daily life. As much as possible, medical decision-making should be evidence-based. However, with limited patient and financial resources, not every question can be addressed with a timely randomized phase III clinical trial. Reasonable extrapolations have to be made in clinical practice. Phase III trials are ongoing to evaluate CapeOx versus FOLFOX in both first- and second-line settings and as adjuvant treatment for metastatic colorectal cancer. While we are waiting for the results of these trials, we think there is

compelling evidence that the CapeOx regimen can replace FOLFOX in the treatment of colorectal cancer and can serve as a backbone for incorporation of innovative targeted agents such as epidermal growth factor receptor and vascular endothelial growth factor monoclonal antibodies and others.

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Pumpin' FU (or, Avoiding That Oral Fixation)

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FOLFOX, consisting of oxaliplatin with LV and infusional 5-FU, is the regulatory and de facto clinical standard of care regimen for the use of oxaliplatin-based therapy in colorectal cancer. The preponderance of evidence-based data, including multiple prospectively randomized clinical trials, support its activity and safety.

Can we make the leap to substitute LV/5-FU with the oral agent capecitabine in combination with oxaliplatin? Is this substitution supported by adequate experimental evidence at this time? Is the use of capecitabine plus oxaliplatin (CapeOx) regimens as a standard of care reasonable, based on its toxicity and activity profile or economic factors? The answer to all these questions is no, not at this time.

Standard of Care

In this discussion, "FOLFOX" will be used as a general term to refer to any one of the biweekly infusion programs of oxaliplatin with LV and 5-FU. The most widely used regimen in pivotal trials has been FOLFOX4 (with LV infusion and 5-FU bolus plus infusion on days 1 and 2). However, most current studies use modified FOLFOX6 with LV given on day 1, followed by 46-hour 5-FU infusion (with or without the 5-FU bolus). Clinical data support equivalence of these regimens.

Studies with FOLFOX include the first-line study by the Groupe d'Etude et de Recherche Clinique en Oncologie at Radiothérapie (GERCOR), which found a 50% improvement in time to progression and a response rate twice that observed among patients receiving LV5FU2 (biweekly infusion).¹ The MOSAIC trial, an international phase III study of more than 2,200 patients, compared FOLFOX to LV5FU2 and demonstrated a 24% reduction in risk of death for patients receiving FOLFOX.²

The toxicity profile observed in the MOSAIC study most clearly demonstrates the relative risks of adding oxaliplatin to 5-FU infusion. The FOLFOX regimen was very safe, with a less than 0.5% mortality rate. Grade 3/4 adverse events included uncomplicated neutropenia

(41%), diarrhea (11%), vomiting (6%), and febrile neutropenia (2%). In comparison, toxicities observed in patients receiving 5-FU/LV alone included neutropenia (5%), diarrhea (7%), and febrile neutropenia (<1%).

A second-line study of 463 patients treated with single-agent oxaliplatin, LV/5-FU infusion, or FOLFOX is one of the very few studies to demonstrate clinical synergy for any regimen, and showed the improved activity for oxaliplatin with LV/5-FU. The response rates for single-agent oxaliplatin and LV/5-FU were both less than 1%; by contrast, the response rate among patients receiving FOLFOX was 10%.³

The above-mentioned controlled trials demonstrate the safety and efficacy of FOLFOX compared with biweekly infusional 5-FU plus LV, the most effective and least toxic way to administer 5-FU.

5-FU/LV Regimens

Infusional 5-FU, as either a 24-hour weekly (the AIO regimen) or biweekly (LV5FU2) dose, is the preferred method for 5-FU administration due to its more acceptable toxicity profile. Studies comparing infusional 5-FU (weekly or bi-weekly) to the Mayo Regimen (5-FU 425 mg/m² IV bolus plus LV 20 mg/m² per day × 5 days) have shown the 5-day bolus schedule to be associated with increased toxicity without a significantly improved benefit.

For example, de Gramont et al⁴ randomized 448 patients to receive either the Mayo regimen or LV5FU2 (biweekly) infusion. The grade 3/4 toxicity rate for patients receiving the Mayo regimen was 24%, versus 11% for patients receiving infusional LV5FU2. Observed adverse events in the Mayo regimen and LV5FU2 groups, respectively, included neutropenia (7% vs 2%), diarrhea (7% vs 3%), and mucositis (7% vs 2%). The response rate for patients receiving the biweekly infusion was 33%, compared with 14% among patients receiving the Mayo regimen.

A Southwest Oncology Group/Eastern Cooperative Oncology group study comparing a weekly high-dose infusion and low-dose continuous infusion confirmed the low incidence of adverse events (<10% grade 3/4 toxicity), efficacy, and feasibility for the infusion schedules in the hands of US physicians.⁵

In light of the increased toxicity observed with the Mayo regimen in comparison with infusional LV/5-FU, it is important to bear in mind that clinical trials of capecitabine conducted to date have employed the Mayo regimen, the most toxic regimen of 5-FU as the comparison arm. Capecitabine has not been compared with infusional 5-FU programs.

Toxicity of Capecitabine and CapeOx

The toxicity rates observed with both LV5FU2 and FOLFOX are considerably lower than those associated with capecitabine as a single agent.⁶ Capecitabine has been evaluated in randomized phase III trials for both first-line therapy of colon cancer and adjuvant therapy in comparison with the Mayo regimen, suggesting acceptable toxicity. However, as noted above, the toxicity profile for the Mayo regimen is greater than for infusional 5-FU. In addition, the approved doses of capecitabine are not well tolerated by US patients and the drug is almost always given at doses below that approved by the US Food and Drug Administration. No efficacy data have been presented at the doses commonly used in practice.⁶

In the recently reported TREE study, patients were randomized to receive FOLFOX, oxaliplatin plus bolus 5-FU, or CapeOx in the TREE-1 cohort (50 patients per arm) and then in combination with bevacizumab (75 patients per arm) in the TREE-2 cohort through a study amendment.⁷ The preliminary results show that 50% of patients receiving CapeOx required a dose reduction within the first 12 weeks, in comparison with 20% of patients receiving FOLFOX or oxaliplatin plus bolus 5-FU. In addition, the incidence of grade 3/4 diarrhea, dehydration, and hospitalizations were higher for the CapeOx arm versus the FOLFOX or oxaliplatin/5-FU arms.

The independent Data and Safety Monitoring Committee reduced the dose of capecitabine from 1,000 mg/m² to 850 mg/m² twice per day in the TREE-2 cohort (when combined with bevacizumab), which improved the toxicity profile considerably. Current randomized studies by Roche, however, continue to use the full-dose CapeOx regimen. More data are needed to determine the ultimate tolerated doses and efficacy of this regimen before it can be used widely, particularly for the US population.

Patient Preference

Studies have suggested patients prefer oral medications over IV administration, but not at the expense of efficacy. While the merits of oral versus IV administration may be debated in current practice situations, this argument is somewhat fallacious when dealing with mixed IV-oral regimens, such as CapeOx. It would be more appropriate to ask a patient, “given that you are receiving intravenous therapy every 2 weeks anyway, would you prefer being connected to the pump at that time for 2 days, or would you prefer to take 3–6 pills twice daily for 14 days?” The difference in preference would most likely be relatively small, even before taking into account the increased diarrhea and hand-foot syndrome for the capecitabine-containing regimen.

Economics of Capecitabine

Capecitabine is expensive. The online retail cost for 1,000 mg/m² twice per day for 14 days is \$1,127.00 (\$11.50 per 500 mg tablet), using assumed body surface area of 1.75 m². In comparison, 5-FU 3,000 mg/m² costs \$10.10 (wholesale price). While many institutions have engaged outside agencies to handle infusion of 5-FU, we routinely use disposable infusers (Baxter Company), which cost \$36.00 and which patients can disconnect on their own. Alternatively, mechanical pumps may be leased (and are reimbursable by Durable Medical Equipment Regional Carriers or third-party payors). Even including these additional expenses, the cost of infusional 5-FU is an order of magnitude less than capecitabine. Given the toxicity and the amount of nursing intervention to manage capecitabine, this agent does not represent an economic strategy for either the patient or the physician.

Conclusion

In conclusion, FOLFOX remains the regimen most heavily supported by the prospective clinical evidence, and should continue to be the standard of care pending the results of new comparative data. The TREE trials suggest a high toxicity profile for the full-dose CapeOx regimen in a US population, with improved tolerance at reduced doses. From an economic standpoint, capecitabine is much more expensive than 5-FU, even including the cost of infusion. Thus, routine use of CapeOx in the treatment of colorectal cancer at this time is premature.

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