Regimen Monograph

A - Regimen Name

XELOX Regimen

Capecitabine (Xeloda®)-Oxaliplatin

Disease Site	Gastrointestinal Colorectal Small bowel and appendix
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Treatment of metastatic colorectal, small bowel and appendiceal cancer
Supplementary Public Funding	**capecitabine** ODB - General Benefit (capecitabine) (ODB Formulary)

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B - Drug Regimen

oxaliplatin	130 mg /m²	IV	Day 1
capecitabine	1000 mg /m²	PO	BID, Days 1 to 14

Note: a dose of 750 mg/m^2 PO BID was used in a small phase 2 study in small bowel cancer (Overman MJ et al.)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate
No routine prophylaxis for capecitabine

Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Oxaliplatin premedication (prophylaxis for infusion reactions):

- There is insufficient evidence that routine prophylaxis with pre-medications reduces IR rates.
- Consider corticosteroids and H1-receptor antagonists ± H2-receptor antagonists in high-risk patients (i.e. ≥ cycle 6, younger age, female gender, prior platinum exposure, platinum-free interval ≥ 3 years).

Other Supportive Care:

- Topical emollients (e.g. hand creams, udder balm) therapy may ameliorate the manifestations of hand-foot syndrome in patients receiving capecitabine.

- Standard antidiarrheal agents (e.g. loperamide) should be initiated, as medically appropriate, as early as possible.
- Patients should be counselled about cold avoidance prior to receiving oxaliplatin, since cold temperatures can precipitate or exacerbate acute neurological symptoms.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Do not retreat until ANC ≥ 1.5 x 10^9 /L, platelet counts ≥ 100 x 10^9 /L and major organ toxicity has resolved to ≤ grade 1.

Oxaliplatin

Neurotoxicity was graded based on the following scales in some metastatic colorectal cancer trials.

Neurotoxicity Grade	Description
1	Resolved and did not interfere with functioning
2	Interfered with function but not daily activities
3	Pain or functional impairment that interfered with daily activities
4	Persistent impairment that is disabling or life-threatening

Dose Modifications

Toxicity Grade	Oxaliplatin Dose^
Persistent[1] Grade 2 neurotoxicity	↓ 25%
Transient[1] Grade 3 neurotoxicity	↓ 25%

Persistent[1] Grade 3 neurotoxicity or any Grade 4 neurotoxicity	Discontinue
≥ Grade 3 GI toxicity (after prophylaxis) OR ≥ Grade 3 Platelets OR ≥ Grade 3 Neutropenia (including febrile neutropenia)	↓ 25%
Sepsis / septic shock	Discontinue
Other ≥ grade 3 related organ toxicity [2]	Consider ↓ 25%
Pharyngolaryngeal dysesthesia	Hold; then increase duration of infusion to 6 hours[3]
Pneumonitis	Hold, investigate; discontinue permanently if confirmed.
Anaphylactic-like reaction	Discontinue
PRES/RPLS	
Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia	
Disseminated intravascular coagulation (DIC)	
QT prolongation	
Intestinal ischemia or duodenal ulcer	
Symptoms of rhabdomyolysis	

^Do not re-treat until the ANC ≥ 1.5 x 10^9/L and the platelets ≥ 100 x 10^9/L, GI and neurotoxicities have resolved and other non-hematologic toxicities ≤ grade 1.

[1] Transient = >7days - <1 cycle; persistent = ≥ 1 cycle

[2] For skin toxicity, reduce capecitabine dose only (see table below)

[3] If oxygen saturation is normal, an anxiolytic agent may be given

Capecitabine

Dose modifications are mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Missed or omitted doses of capecitabine should not be replaced. Doses should not be re-escalated if reduced for toxicity.

Toxicity	Action During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2 1st appearance 2nd appearance 3rd appearance 4th appearance	 Hold until resolved to ≤ grade 1 Hold until resolved to ≤ grade 1 Hold until resolved to ≤ grade 1 Discontinue treatment permanently	 100% 75% 50% Not applicable
Grade 3 1st appearance 2nd appearance 3rd appearance OR any evidence of Stevens-Johnson syndrome (i.e. sloughing)	 Hold until resolved to ≤ grade 1 Hold until resolved to ≤ grade 1 Discontinue treatment permanently	 75% 50% Not applicable
Grade 4 1st appearance 2nd appearance	 Discontinue permanently or If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to ≤ grade 1. Discontinue permanently	 Discontinue or 50% Not applicable

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Oxaliplatin:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate	• Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.

* Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist).

Hepatic Impairment

Hepatic Impairment	Oxaliplatin (% previous dose)	Capecitabine (% previous dose)*
Mild	No dose adjustment required	No starting dose adjustment necessary
Moderate		
Severe	No data available	No data available

*use capecitabine dose modification table above for hepatotoxicity during treatment

Renal Impairment

Creatinine Clearance (mL/min)	oxaliplatin (% previous dose)	capecitabine (% previous dose)
≥50	No change	100%, with close monitoring
30 to <50	Caution	75 % (use with caution)
<30	Discontinue	CONTRAINDICATED

Dosage in the Elderly

For oxaliplatin, patients ≥ 65 years had a higher incidence of GI toxicity, myelosuppression, syncope and fatigue. No dose adjustments were needed but caution should be exercised.

For capecitabine, older patients are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3 / 4 adverse effects, especially when used in combination. Starting dosage adjustment is not recommended, but dose modifications should be performed for toxicity (see tables above).

Dosage based on gender:

Females were observed to have higher number of severe adverse effects with oxaliplatin than males.

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F - Adverse Effects

Refer to oxaliplatin, capecitabine drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Sensory neuropathy (may be severe) • Myelosuppression +/- infection, bleeding (may be severe) • Nausea, vomiting • Hand-foot syndrome • Increased LFTs (may be severe) • Diarrhea (may be severe)	• Fatigue • Mucositis • Pharyngolaryngeal dysesthesia (with oxaliplatin) • Alopecia (generally mild)	• Constipation • ↑ Bilirubin • Edema • Rash • Hyperglycemia • Musculoskeletal pain • Anorexia • Weight changes • Dysgeusia • Injection-site reactions (with oxaliplatin) • Abnormal electrolytes • Hypersensitivity	• Arterial/Venous thromboembolism • QT interval prolonged • Cardiotoxicity • GI obstruction, perforation • INR / prothrombin increased • Disseminated intravascular coagulation • Hemolytic uremic syndrome • Hemolysis • Idiopathic thrombocytopenic purpura • Hepatic failure • Nephrotoxicity • Pancreatitis • Pneumonitis • Rhabdomyolysis • PRES/RPLS • Leukoencephalopathy • Veno-occlusive disease • Guillain-Barre syndrome • Eye disorders

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G - Interactions

Refer to oxaliplatin, capecitabine drug monograph(s) for additional details

- Concomitant use with sorivudine or analogues is **contraindicated**, given the increased risk of capecitabine toxicity (may be fatal). Wait at least 4 weeks after sorivudine (or chemically related analogues) treatment before starting capecitabine.
- Avoid concomitant administration with phenytoin; capecitabine may increase levels. Monitor phenytoin levels if must be given together.
- Monitor PT/INR when this treatment is administered with warfarin or other anticoagulants; adjust anticoagulant dose accordingly.
- Caution with the use of proton pump inhibitors and monitor for reduced effectiveness of capecitabine; consider switching to a magnesium and aluminum hydroxide-containing antacid.
- Caution and monitor with the coadministration of leucovorin as this may increase capecitabine toxicity.
- Monitor for toxicity when using oxaliplatin with other nephrotoxic drugs, QT-prolonging drugs or drugs associated with rhabdomyolysis.

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H - Drug Administration and Special Precautions

Refer to oxaliplatin, capecitabine drug monograph(s) for additional details

Administration:

Oxaliplatin

- Oxaliplatin is administered by intravenous infusion.
- May be mixed in 250-500 mL bag (D5W only). **Do not** mix with NS, chloride containing or alkaline solutions.
- Administer by slow infusion. Concentration must be between 0.2 to 0.7 mg/mL.
- Infuse IV over 2 hours. Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia.
- Do not mix oxaliplatin with other drugs in the same infusion bag or infusion line.
- If another drug is given before oxaliplatin, flush infusion line with D5W before giving oxaliplatin. Flush the line with D5W after oxaliplatin before giving a subsequent drug.
- The compatibility of oxaliplatin solution for infusion has been tested with representative, PVC-based, administration sets.
- Do not use with injection equipment containing aluminum, as this can degrade platinum compounds.
- Unopened vials should be stored at 15-30°C; protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Capecitabine

- Oral self-administration; drug available by outpatient prescription.
- Doses are given orally approximately 12 hours apart, within 30 minutes after the end of a meal.
- Swallow tablets whole; do not crush or cut tablets.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package.

Contraindications:

- Patients who have a known hypersensitivity to capecitabine, 5-fluorouracil, oxaliplatin, other platinum agents (e.g. cisplatin), or any ingredient in the formulation or component of the container
- Patients with severe renal impairment (CrCl <30 mL/min)
- Patients who are pregnant or breastfeeding
- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Concomitant use with sorivudine or related analogues (i.e. brivudine), given potential fatal drug interaction.

Warnings/Precautions:

- Patients should be counselled about cold avoidance prior to receiving oxaliplatin, since cold temperatures can precipitate or exacerbate acute neurological symptoms.
- Oxaliplatin may cause dizziness or visual disturbances in some patients (including transient vision loss); patients should exercise caution when driving or operating machinery.
- Use with caution in patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents
- Use with caution in patients with a history of cardiovascular disease as well as patients taking anticoagulants such as warfarin (see Drug Interactions section)
- Use capecitabine with extreme caution in patients with partial DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Capecitabine contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders.

Pregnancy/Lactation:

- This regimen is **contraindicated** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is **contraindicated** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Yes

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline and before each cycle
- Liver and renal function tests; Baseline and before each cycle
- Electrolytes, including magnesium; Baseline and before each cycle
- INR and/or PT; Baseline and as clinically indicated if on anticoagulants
- Clinical toxicity assessment of GI effects, dehydration, neurotoxicity, infection, bleeding, thromboembolism, hypersensitivity, injection site reaction, rash, hand-foot syndrome, cardiac, respiratory and ophthalmic effects; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration (capecitabine)

Approximate Patient Visit	2 hours
Pharmacy Workload (average time per visit)	17.14 minutes
Nursing Workload (average time per visit)	44.167 minutes

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K - References

Capecitabine and oxaliplatin drug monographs, Cancer Care Ontario.

BCCA protocol summary for palliative combination chemotherapy for metastatic colorectal cancer using oxaliplatin and capecitabine, Oct 2008.

Cassidy J, Clarke S, Dı´az-Rubio E, et al. XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br J Cancer 2011; 105: 58–64.

Cassidy J, Clarke S, Diaz-Rubio E et al. Randomized Phase III Study of Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid Plus Oxaliplatin As First-Line Therapy for Metastatic Colorectal Cancer. J Clin Oncol 2008; 26: 2006-2012.

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National Comprehensive Cancer Network. Colon Cancer (Version 2.2017). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed June 30, 2017.

Overman MJ, Varadhachary GR, Kopetz S et al. Phase II Study of Capecitabine and Oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of vater. JCO 2009; 27(16):2598-2603.

Rothenberg ML, Cox JV, Butt C, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: a randomized phase III noninferiority study. Annals of Oncology 2008; 19: 1720–6.

Zaanan A, Costes L, Gaauthier M et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicentre AGEO study. Ann Oncol 2010; 21: 1786-93.

PEBC Advice Documents or Guidelines

- Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent
- Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer

November 2023 Modified Pregnancy/lactation section

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the

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Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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