# MFOLFOX6 Regimen

**Folinic Acid (Leucovorin)-Fluorouracil-Oxaliplatin**

| Disease Site | Gastrointestinal - Colorectal  
|             | Gastrointestinal - Small bowel and appendix |
| Intent      | Adjuvant |
| 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**

- Adjuvant treatment of stage III or high risk stage II colorectal, small bowel or appendiceal cancer
- Perioperative chemotherapy for metastatic colorectal, small bowel and appendiceal cancer patients deemed by a standards compliant Multidisciplinary Cancer Conference ([MCC](#)) or equivalent, to have the following metastases that are resectable or potentially resectable:
  - Liver metastases\(^1\), OR
  - Lung metastases\(^2\), OR
  - Liver and lung metastases\(^2\); OR
  - Liver and non-pulmonary extrahepatic metastases\(^2\)
Supplementary Public Funding

oxaliplatin
New Drug Funding Program (Oxaliplatin - Adjuvant Colorectal Small Bowel or Appendiceal Cancer)

oxaliplatin
New Drug Funding Program (Oxaliplatin - With Surgery for Curative Intent for CRC SBAC Pts with Resectable or Potentially Resectable Liver Mets) \(^{(1)}\)

oxaliplatin
Evidence Building Program (Oxaliplatin (EBP) - Colorectal Cancer Patients with Resectable or Potentially Resectable Extrahepatic Metastases) \(^{(2)}\) excludes small bowel or appendiceal cancer

oxaliplatin
Evidence Building Program (Oxaliplatin (EBP) - Supplemental 1) \(^{(2)}\) excludes small bowel or appendiceal cancer

oxaliplatin
Evidence Building Program (Oxaliplatin (EBP) - Supplemental 2) \(^{(2)}\) excludes small bowel or appendiceal cancer

B - Drug Regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Administration</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxaliplatin</td>
<td>85 mg/m²</td>
<td>IV in 500mL D5W over 120 minutes</td>
<td>Day 1</td>
</tr>
<tr>
<td>leucovorin</td>
<td>400 mg/m²</td>
<td>IV diluted in D5W over 120 minutes (concurrently with oxaliplatin)</td>
<td>Day 1</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>400 mg/m²</td>
<td>IV bolus, after leucovorin</td>
<td>Day 1</td>
</tr>
<tr>
<td><em>THEN</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluorouracil</td>
<td>2400 mg/m²</td>
<td>IV continuous infusion Start on Day 1 over 46 hours (single dose)</td>
<td></td>
</tr>
</tbody>
</table>
**C - Cycle Frequency**

**REPEAT EVERY 14 DAYS**

**Adjuvant:** Maximum 12 cycles unless disease progression or unacceptable toxicity occurs

**Resectable or potentially resectable metastases:** A randomized controlled trial has used 6 cycles before surgery and 6 cycles post-surgery (funded by NDFP for up to 12 cycles, given as pre-op, post-op or perioperatively as “pre- and post-op”). Patients who progress on FOLFOX may be transitioned over to other appropriate first-line metastatic regimens (Refer to January 8, 2013 funding announcement).

**D - Premedication and Supportive Measures**

**Antiemetic Regimen:** Moderate

**Febrile Neutropenia**

**Risk:** Low

**Other Supportive Care:**

Also refer to [CCO Antiemetic Summary](#)

**E - Dose Modifications**

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

**Dosage with toxicity**

See [appendix 6](#) for general recommendations for hematologic toxicity. No dose adjustments required for leucovorin.

**Neurotoxicity** was graded based on the following scales in some adjuvant colorectal cancer trials.
### Neurotoxicity Grade Description

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No change or none</td>
</tr>
<tr>
<td>2</td>
<td>Mild paresthesias, loss of deep tendon reflexes</td>
</tr>
<tr>
<td>3</td>
<td>Mild or moderate objective sensory loss, moderate paresthesias</td>
</tr>
<tr>
<td>4</td>
<td>Severe objective sensory loss or paresthesias that interfere with function</td>
</tr>
</tbody>
</table>

### Dose Modifications:

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Oxaliplatin^</th>
<th>Fluorouracil^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent(1) Grade 2 Neurotoxicity</td>
<td>↓ from 85 → 75 mg/m²</td>
<td>No change</td>
</tr>
<tr>
<td>Transient(1) Grade 3 Neurotoxicity</td>
<td>↓ from 85 → 75 mg/m²</td>
<td>No change</td>
</tr>
<tr>
<td>Persistent(1) ≥ Grade 3 Neurotoxicity or any Grade 4 Neurotoxicity</td>
<td>Discontinue</td>
<td>No change</td>
</tr>
<tr>
<td>≥ Grade 3 GI toxicity (after prophylaxis) OR Grade 3 or 4 Platelets OR Grade 3 or 4 Neutropenia (including febrile neutropenia)*</td>
<td>↓ from 85 → 75 mg/m² *</td>
<td>Reduce by 20% *</td>
</tr>
<tr>
<td>Sepsis / septic shock</td>
<td>Discontinue</td>
<td>Discontinue</td>
</tr>
<tr>
<td>Other ≥ grade 3 related organ toxicity(2)</td>
<td>↓ from 85 → 75 mg/m²</td>
<td>Reduce by 20%</td>
</tr>
<tr>
<td>Pharyngolaryngeal dysesthesia</td>
<td>Hold; then increase duration of infusion to 6 hours(3)</td>
<td>No change</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Hold, investigate; discontinue permanently if confirmed.</td>
<td></td>
</tr>
<tr>
<td>RPLS or Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia</td>
<td>Discontinue permanently</td>
<td></td>
</tr>
</tbody>
</table>

^Do not re-treat until the ANC ≥ 1.5 x 10⁹/L and the platelets ≥ 75-100 x 10⁹/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 5FU dose only
If oxygen saturation is normal, an anxiolytic agent may be given.
* Discontinue if sepsis/septic shock.

### Hepatic Impairment

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>AST/ALT</th>
<th>oxaliplatin (% previous dose)</th>
<th>fluorouracil (% previous dose)</th>
<th>leucovorin (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 x ULN</td>
<td></td>
<td>No change</td>
<td>Caution</td>
<td>No change</td>
</tr>
<tr>
<td>&gt;2-4 x ULN</td>
<td>And/or</td>
<td>2-4 x ULN</td>
<td>No change</td>
<td>Caution</td>
</tr>
<tr>
<td>&gt;4 x ULN</td>
<td>And/or</td>
<td>4 x ULN</td>
<td>No data available</td>
<td>OMIT if Bilirubin &gt; 4 x ULN</td>
</tr>
<tr>
<td>ANY</td>
<td>Or</td>
<td>&gt; 4 X ULN</td>
<td>No data available</td>
<td>OMIT if Bilirubin &gt; 4 x ULN</td>
</tr>
</tbody>
</table>

### Renal Impairment

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>oxaliplatin (% previous dose)</th>
<th>fluorouracil (% previous dose)</th>
<th>leucovorin (% previous dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 - 80</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>30 - &lt;50</td>
<td>Caution</td>
<td>No change; monitor</td>
<td>No change</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Discontinue</td>
<td>Consider dose ↓</td>
<td>No change</td>
</tr>
</tbody>
</table>

back to top

F - Adverse Effects
Refer to oxaliplatin, leucovorin, fluorouracil drug monograph(s) for additional details of adverse effects.

<table>
<thead>
<tr>
<th>Very common (≥ 50%)</th>
<th>Common (25-49%)</th>
<th>Less common (10-24%)</th>
<th>Uncommon (&lt; 10%), but may be severe or life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sensory neuropathy (may be severe, including cranial)</td>
<td>• Fatigue</td>
<td>• Anorexia, weight changes</td>
<td>• Venous / arterial thromboembolism</td>
</tr>
<tr>
<td>• Myelosuppression ± infection, bleeding</td>
<td>• Mucositis (may be severe)</td>
<td>• Abdominal pain</td>
<td>• QT prolongation, arrhythmia</td>
</tr>
<tr>
<td>• Nausea, vomiting</td>
<td>• Pharyngolaryngeal dysesthesia</td>
<td>• Constipation</td>
<td>• Cardiotoxicity</td>
</tr>
<tr>
<td>• ECG changes (mostly asymptomatic)</td>
<td>• Alopecia (mostly mild)</td>
<td>• Edema</td>
<td>• Guillain-Barre syndrome</td>
</tr>
<tr>
<td>• ↑ LFTs</td>
<td></td>
<td>• Hyperglycemia</td>
<td>• Optic neuritis</td>
</tr>
<tr>
<td>• Diarrhea (may be severe)</td>
<td></td>
<td>• Musculoskeletal pain</td>
<td>• Extrapyramidal or cortical dysfunction, acute cerebellar syndrome</td>
</tr>
</tbody>
</table>

- Rash, Hand-foot syndrome
- Dysgeusia
- Injection site reaction
- Abnormal electrolyte(s)
- Hypersensitivity
- Venous / arterial thromboembolism
- QT prolongation, arrhythmia
- Cardiotoxicity
- Guillain-Barre syndrome
- Optic neuritis
- Extrapyramidal or cortical dysfunction, acute cerebellar syndrome
- RPLS / PRES
- Leukoencephalopathy
- Nephrotoxicity
- Pneumonitis
- INR / prothrombin time increased
- Disseminated intravascular coagulation
- Hemolysis
- Hemolytic uremic syndrome
- Idiopathic thrombocytopenic purpura
- Photosensitivity
- Radiation recall reaction
- GI obstruction / perforation / ulcer / ischemia
- Pancreatitis
- Veno-occlusive disease
- Rhabdomyolysis
- Hearing impaired
- Eye disorders

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G - Interactions

Refer to oxaliplatin, leucovorin, fluorouracil drug monograph(s) for additional details.

H - Drug Administration and Special Precautions

Refer to oxaliplatin, leucovorin, fluorouracil drug monograph(s) for additional details.
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.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Electrolytes, including magnesium; baseline and regular
- INR, if patient on anticoagulants; baseline and regular
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Clinical assessment of GI effects, neurotoxicity, infection, bleeding, stomatitis, diarrhea, skin effects, thromboembolism, hypersensitivity, local reactions, respiratory or ophthalmic effects; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

J - Administrative Information

Approximate Patient Visit 3 hours
Pharmacy Workload (average time per visit) 38.381 minutes
Nursing Workload (average time per visit) 69.167 minutes

K - References


Oxaliplatin, fluorouracil and leucovorin drug monographs, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- The Role of Liver Resection in Colorectal Cancer Metastases
- Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection
- Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer

August 2019 removed archived PEBC guideline link

L - Other Notes

Perioperative Chemotherapy in Liver Metastases:

The randomized controlled trial by Nordlinger et al showed a non-significant 7.3% improvement in PFS in all randomized patients at three years in the surgery plus chemotherapy group versus surgery alone. Re-analysis of the subset of patients who were eligible to enter the trial or received resection indicated a significant increase in PFS. Reversible postoperative complications occurred significantly more often after chemotherapy than with surgery alone. Perioperative chemotherapy reduced the relative risk of relapse by one quarter.

A pooled analysis of two smaller studies of 5FU postoperative chemotherapy showed trends in PFS and overall survival favouring the surgery plus chemotherapy group that did not reach statistical significance.
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 information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

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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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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