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 completely resected stage III or high risk† stage II colon or rectal cancer where oxaliplatin is given in combination with 5-fluorouracil and leucovorin (†eligible high risk factors include: obstruction, perforation, poorly differentiated adenocarcinoma, inadequate lymph node sampling or T4 tumour)
- Perioperative chemotherapy for metastatic colorectal 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 metastases¹, OR
  - Lung metastases², OR
  - Liver and lung metastases²; OR
  - Liver and non-pulmonary extrahepatic metastases²
Supplementary Public Funding

oxaliplatin
New Drug Funding Program (Oxaliplatin - Adjuvant High Risk Stage II Colon Cancer) \(\text{[NDFP Website]}\)

oxaliplatin
New Drug Funding Program (Oxaliplatin - Adjuvant High Risk Stage II Rectal Cancer)

oxaliplatin
New Drug Funding Program (Oxaliplatin - Adjuvant Stage III Colon Cancer)

oxaliplatin
New Drug Funding Program (Oxaliplatin - Adjuvant Stage III Rectal Cancer)

oxaliplatin
New Drug Funding Program (Oxaliplatin - With Surgery for Colorectal Cancer with Resectable or Potentially Resectable Liver Metastases) \(^1\)

oxaliplatin
Evidence Building Program (Oxaliplatin (EBP) - Colorectal Cancer Patients with Resectable or Potentially Resectable Extrahepatic Metastases) \(^2\)

oxaliplatin
Evidence Building Program (Oxaliplatin (EBP) - Supplemental 1) \(^2\)

oxaliplatin
Evidence Building Program (Oxaliplatin (EBP) - Supplemental 2) \(^2\)

B - Drug Regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</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>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>1</td>
</tr>
</tbody>
</table>
**fluorouracil**

**THEN**

400 mg /m² IV bolus, after leucovorin  
Day 1

**fluorouracil**

2400 mg /m² IV continuous infusion  
Start on Day 1 
over 46 hours (single dose)

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**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).

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**D - Premedication and Supportive Measures**

**Antiemetic Regimen:** Moderate

**Febrile Neutropenia Risk:** Low

**Other Supportive Care:**

Also refer to [CCO Antiemetic Summary](#)

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**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.

<table>
<thead>
<tr>
<th>Neurotoxicity Grade</th>
<th>Adjuvant</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/m^2</td>
<td>No change</td>
</tr>
<tr>
<td>Transient (1) Grade 3 Neurotoxicity</td>
<td>↓ from 85 → 75 mg/m^2</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/m^2 *</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/m^2</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>
</tbody>
</table>
**Pneumonitis**

Hold, investigate; discontinue permanently if confirmed.

**RPLS or Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia**

Discontinue permanently

^Do not re-treat until the ANC ≥ 1.5 x 10^9/L and the platelets ≥ 75-100 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 5FU dose only
3 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 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>No change</td>
<td>Caution</td>
<td>No change</td>
</tr>
<tr>
<td>&gt;2-4 x ULN</td>
<td>And/or 2-4 x ULN</td>
<td>No change</td>
<td>Caution</td>
</tr>
<tr>
<td>&gt;4 x ULN</td>
<td>And/or 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 &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>
F - Adverse Effects

Refer to [oxaliplatin](#), [leucovorin](#), [fluorouracil](#) drug monograph(s) for additional details of adverse effects.

<table>
<thead>
<tr>
<th>Most Common Side Effects</th>
<th>Less Common Side Effects, but may be Severe or Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neuropathy (may be severe)</td>
<td>• Arterial thromboembolism</td>
</tr>
<tr>
<td>• Nausea, vomiting</td>
<td>• Venous thromboembolism</td>
</tr>
<tr>
<td>• ↑ LFTs (may be severe)</td>
<td>• Hypersensitivity</td>
</tr>
<tr>
<td>• Diarrhea (may be severe)</td>
<td>• Cardiotoxicity</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>• Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>• Mucositis</td>
<td>• Nephrotoxicity</td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td>• Myelosuppression ± infection, bleeding (may be severe)</td>
<td>• Pneumonitis</td>
</tr>
<tr>
<td>• Rash, hand-foot syndrome</td>
<td>• Rhabdomyolysis</td>
</tr>
<tr>
<td>• Pharyngolaryngeal dysesthesia</td>
<td>• RPLS</td>
</tr>
</tbody>
</table>

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

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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.

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


Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of...
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.

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**Peri-operative Chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial.**


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

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**PEBC Advice Documents or Guidelines**

- [The Role of Liver Resection in Colorectal Cancer Metastases](#)

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