**mFOLFOX6**

**Oxaliplatin, Leucovorin, Fluorouracil**

**INDICATION**

Metastatic colorectal cancer; adjuvant therapy for stage III colon cancer; adjuvant therapy for rectal cancer; advanced or metastatic rectal cancer.

**DOSAGE AND SCHEDULING**

**CHEMOTHERAPY REGIMEN**

*Cycled every 14 days for 12 cycles, or until disease progression or unacceptable toxicity*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucovorin*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2400 mg/m² IVF over 46-48 hrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Modified from reference 1 (Hochster HS et al. 2008): leucovorin 350 mg/m² IV over 2 hrs, fluorouracil 2400 mg/m² continuous infusion over 46 hrs.

**SUPPORTIVE MEDICATIONS**

**Prophylaxis of acute and delayed emesis**

<table>
<thead>
<tr>
<th>Emetogenicity</th>
<th>Antiemetics</th>
<th>Acute emesis</th>
<th>Acute (5-FU)/delayed (oxaliplatin) emesis</th>
<th>Delayed emesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate risk (day 1)</td>
<td>5-HT3 antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (day 2)</td>
<td>Corticosteroid</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pre-medications to prevent acute emesis on day 1**

- **Corticosteroid**: Dexamethasone 8 mg IV, 30 mins before chemotherapy, day 1
- **5-HT3 antagonist**: Palonosetron 0.25 mg IV, 30 mins before chemotherapy (preferred)

*If palonosetron is not available, substitute a 1st generation 5-HT3 antagonist:*

- **Granisetron**: Granisetron 1 mg (0.01mg/kg) IV, 30 mins before chemotherapy, OR
- **Tropisetron**: Tropisetron 5 mg IV, 30 mins before chemotherapy, OR

**Prevent acute & delayed emesis on days 2-3**

- **Corticosteroid**: Dexamethasone 8 mg PO/IV, day 2-3

**DOSAGE MODIFICATIONS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
</table>
| Oxaliplatin | Clcr ≥30 mL/min: No dosage adjustment necessary.  
Clcr <30 mL/min: Reduce dose from 85 mg/m² to 65 mg/m². | ---                              |
| Fluorouracil | ---                                                                 | Bilirubin >5 mg/dL: Avoid use. |
| Leucovorin    | ---                                                                              | ---                              |
Adjustment for toxicities\textsuperscript{5,6}

\textbf{Oxaliplatin}

- **Neurosensory events:**
  1. Grade 2, persistent (> 7 days): Adjuvant treatment of stage III colon cancer, reduce dose to 75 mg/m\(^2\). Advanced colorectal cancer, reduce dose to 65 mg/m\(^2\). Consider withholding oxaliplatin for grade 2 neuropathy lasting > 7 days despite dose reduction.
  2. Grade 3, persistent (> 7 days):
     \begin{itemize}
     \item \textit{U.S. labeling:} Consider discontinuing oxaliplatin.
     \item \textit{Canadian labeling:} Adjuvant treatment of stage III colon cancer: discontinue oxaliplatin. Advanced colorectal cancer: reduce dose to 65 mg/m\(^2\); if not resolved prior to next cycle, then discontinue.
     \end{itemize}

- **Gastrointestinal toxicity** (grade 3/4): Delay next dose until recovery from toxicity, then reduce dose to 75 mg/m\(^2\) for adjuvant treatment of stage III colon cancer and 65 mg/m\(^2\) for advanced colorectal cancer.

- **Hematologic toxicity** (grade 4 neutropenia or grade 3/4 thrombocytopenia):
  1. Adjuvant treatment of stage III colon cancer: Delay next dose until neutrophils recover to ≥ 1500/mm\(^3\) and platelets recover to ≥ 75,000/mm\(^3\), then reduce dose to 75 mg/m\(^2\).
  2. Advanced colorectal cancer: Delay next dose until neutrophils recover to ≥ 1500/mm\(^3\) and platelets recover to ≥ 75,000/mm\(^3\), then reduce dose to 65 mg/m\(^2\).

- **Pulmonary toxicity** (unexplained respiratory symptoms including nonproductive cough, dyspnea, crackles, pulmonary infiltrates): Discontinue until interstitial lung disease or pulmonary fibrosis have been excluded.

\textbf{Fluorouracil}

- **According to the manufacturer, treatment should be discontinued for the following:**
  Stomatitis or esophagopharyngitis, leukopenia (WBC < 3500/mm\(^3\)), rapidly falling white blood cell count, intractable vomiting, diarrhea, frequent bowel movements, watery stools, gastrointestinal ulcer or bleeding, thrombocytopenia (platelets < 100,000/mm\(^3\)), hemorrhage.

\textbf{PREPARATION}\textsuperscript{5,6}

\begin{itemize}
\item **Oxaliplatin**
  - Diluted in 250-250 mL D5W; do not use NS. (Do not use chloride-containing solution for dilution)
\item **Fluorouracil**
  - IV push: needs no further dilution; IV infusion: dilute in NS or D5W.
\item **Leucovorin**
  - Diluted in D5W or NS for infusion. When leucovorin, oxaliplatin are given concurrently via a Y-connector, both drugs should be administered in D5W.
\end{itemize}

\textbf{ADMINISTRATION}\textsuperscript{5,6}

\begin{itemize}
\item **Oxaliplatin**
  - Infused over 2-6 hrs
  - Do not mix with or administer simultaneously through the same line with alkaline medications (including 5-FU).
  - Flush infusion lines with D5W prior to administration of any concomitant drug.
\item **Leucovorin**
  - Given concurrently with oxaliplatin. When leucovorin, oxaliplatin are given concurrently via a Y-connector, both drugs should be administered in D5W.
  - Because of calcium content of leucovorin, the infusion rate should not exceed 160mg/min.
\item **Fluorouracil**
  - Administered as a slow IV push over 3-5 mins followed by IV infusion.
\end{itemize}

\textbf{MONITORING PARAMETERS}\textsuperscript{1,5}

Monitoring parameters before entering the regimen:

- CBC with differential and platelet count.
- Renal function and liver function tests.
- Hepatitis B/C status.
Monitoring parameters before each course and recommended pretreatment value:\n
- ANC ≥ 1500/μL;
- Platelet count ≥ 100,000/μL;
- AST and ALT ≤ 3X the upper limit of normal;
- Total bilirubin ≤ 2X the upper limit of normal;
- Creatinine ≤ 1.5X the upper limit of normal

CONTRAINDICATIONS\(^5,6\):

- Hypersensitivity to oxaliplatin, leucovorin, fluorouracil, capecitabine, or other platinum compounds, or any component of the formulations
- Pregnancy (risk category: oxaliplatin/D; leucovorin/C; fluorouracil/X) and breast feeding
- Bone marrow depression
- Poor nutritional state
- Serious infection
- Megaloblastic anemias due to vitamin B12 deficiency
- Pernicious anemias due to vitamin B12 deficiency

ADVERSE REACTIONS\(^1,5,6\):

Regimen\(^1\):

- Gastrointestinal: nausea and vomiting (31%), diarrhea (31%)
- Hematologic: neutropenia (53%), anemia (8%)
- Neurologic: paresthesia (18%), hand-foot syndrome (8%)
- Others: fatigue (8%), dehydration (8%)

Oxaliplatin (>10% or rare but fatal):

- Central nervous system: fatigue (61%), fever (25%), pain (14%), headache (13%), insomnia (11%)
- Gastrointestinal: nausea (64%), diarrhea (46%), vomiting (37%), abdominal pain (31%), constipation (31%), anorexia (20%), stomatitis (14%)
- Hematologic: anemia (64%; grades 3/4: 1%), thrombocytopenia (30%; grades 3/4: 3%), leukopenia (13%)
- Hepatic: AST increased (54%; grades 3/4: 4%), ALT increased (36%; grades 3/4: 1%), total bilirubin increased (13%; grades 3/4: 5%)
- Neuromuscular & skeletal: peripheral neuropathy (may be dose limiting; 76%; acute 65%; grades 3/4: 5%; persistent 43%; grades 3/4: 3%), back pain (11%)
- Respiratory: dyspnea (13%), cough (11%)
- Immunologic: anaphylaxis, hypersensitivity reaction

Fluorouracil:

- Cardiovascular: angina, cardiotoxicity, coronary arteriosclerosis, EKG finding, thrombophlebitis.
- Dermatologic: alopecia, hand-foot syndrome (13-43%), maculopapular eruption, pruritic, photosensitivity.
- Gastrointestinal: diarrhea, esophagopharyngitis, loss of appetite, nausea and vomiting, stomatitis, gastrointestinal ulcer.
- Neurologic: headache, cerebellar syndrome, acute, nystagmus
- Hematologic: bleeding, myelosuppression, anemia, leukopenia, thrombocytopenia
- Immunologic: anaphylaxis, immune hypersensitivity reaction

Leucovorin:

- Dermatologic: rash, pruritus, erythema, urticaria.
- Hematologic: thrombocytosis
- Respiratory: wheezing
- Miscellaneous: allergic reactions, anaphylactoid reaction
**NHI REIMBURSEMENT INFORMATION**

**Oxaliplatin:** (89/7/1，91/10/1，93/8/1，98/2/1，98/7/1)

1. 和 5-FU 和 folinic acid 併用

   (1) 治療轉移性結腸直腸癌，惟若再加用 irinotecan（如 Campto）則不予給付。(91/10/1)

   (2) 作為第三期結腸癌 (Duke's C) 原發腫瘤完全切除手術後的輔助療法。(98/2/1 起實施)

**PRODUCT INFORMATION**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brand name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>Eloxatin Concentrate for Solution for Infusion</td>
<td>100 mg/20 mL/vial, 50 mg/10 mL/vial</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>Leucovorin Injection</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Fluoro-uracil 有利癌注射劑</td>
<td>1 g/20 mL/vial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Reconstitution &amp; stability</th>
<th>Dilution &amp; stability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conc.</td>
<td>Room temp.</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucovorin</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

**PATIENT INFORMATION**

**一般注意事項：請參見 “化學治療一般注意事項”**

**特殊注意事項**

**Fluorouracil**

- 可能會對比較敏感，較易膿傷。請使用防曬產品，並以衣服及太陽眼鏡保護避免膿傷。
- 藥物輸注期間，如有胸悶或呼吸困難，請通知護理人員，如有意識變化，請告知醫師，檢測血中 ammonia 濃度。以靜脈滴注輸注給子也較常發生腹瀉與胃腸道症狀。
- 手足症候群又稱為肢端紅腫症。某些化學治療藥少量由微血管滲透到手掌及腳掌的皮膚時，就會產生這種症狀。當患部接觸到熱源或摩擦，會讓症狀惡化造成發紅、疼痛及脱皮的現象，也可能會有麻木或刺痛感。嚴重時會影響日常生活。如有此症狀，請告知醫師。

**Oxaliplatin**

- 接觸到冷的東西或冷空氣可能會使手腳感覺刺痛或麻木。請於注射藥品後至少五天避免暴露於寒冷溫度中，不要食用冷的食物或飲料，或接觸冰箱、冷凍庫或冰冷的地板。
- 若必須接觸冷空氣或冷的物件時，請盡量戴手套。若必須外出，請將皮膚及鼻、口包覆好。在有冷氣的室內或車中時，應盡量著長袖上衣及長褲。
- 若您的手臂，手掌，腿或腳有燒灼感、麻木、刺痛或疼痛感，請告知您的醫師。

**REFERENCES**