FOLFIRINOX

Indication: First-line palliative chemotherapy for metastatic pancreatic cancer with PS 0 - 1

Regimen details: Oxaliplatin 85mg/m² IV D1
Folinic acid 700mg IV D1
Irinotecan 180mg/m² IV D1
5-Fluorouracil 400mg/m² IV D1
5-Fluorouracil 2400mg/m² IVI over 46 hours

Administration: Oxaliplatin in 250ml Glucose 5% over 2 hours
Folinic acid in 250ml Sodium Chloride 0.9% over 2 hours
Irinotecan in 250ml Sodium Chloride 0.9% over 90 minutes, start 30 minutes after folinic acid, using a Y-connector
5FU bolus injection over 5 minutes
5FU infusion either via central venous catheter and ambulatory infusion device over 46 hours or continuous peripheral IV infusion over 46 hours, given in 2 x 1 litre Sodium Chloride 0.9%

Frequency: 2 weekly for 6 cycles, then CT scan and clinical review
Maximum of 12 cycles

Extravasation: Non-vesicant

Anti-emetics: Highly emetogenic
Follow local anti-emetic policy

Supportive medication: Mouthcare as per local policy
Loperamide 4mg stat then 2mg PRN until diarrhoea free for at least 12 hours
Ciprofloxacin PO 250mg BD for 5 days if diarrhoea persists for >24hours
GCSF as per local policy

Regular investigations: FBC D1
U&Es D1
LFTs D1
CEA 4 weekly
CT scan after 6 cycles
Consider weekly FBC in patients at high risk of neutropenia.

Toxicities: Myelosuppression, diarrhoea (see comments), nausea and vomiting, mucositis, neurotoxicity, allergic reactions (see comments), alopecia, fatigue, cholinergic syndrome (see comments), palmar-plantar erythema (PPE), coronary artery spasm (see comments), acute dysaesthesia (see comments), ovarian failure/infertility, interstitial pulmonary disease (uncommon)
DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils <1.5 x 10^9/L
or
Platelets <75 x 10^9/L
Delay treatment for 1 week.
Repeat FBC and, if recovered to above these levels
resume treatment as below:

<table>
<thead>
<tr>
<th>Neutrophils &lt; 1.5 x 10^9/L</th>
<th>Oxaliplatin</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Give 100% dose</td>
<td>Reduce to 150mg/m²</td>
<td>Omit 5FU bolus</td>
</tr>
<tr>
<td>2nd occurrence*</td>
<td>Reduce to 60mg/m²</td>
<td>Maintain 150mg/m² dose</td>
<td></td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Discontinue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For any episode of febrile neutropenia, or recurrent grade 3/4 neutropenia despite a first-dose reduction, consider GCSF prophylaxis with subsequent cycles starting on day 5 of each cycle.

<table>
<thead>
<tr>
<th>Platelets &lt; 75 x 10^9/L</th>
<th>Oxaliplatin</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Give 100% dose</td>
<td>Give 100% dose</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Reduce to 60mg/m²</td>
<td>Reduce to 60mg/m²</td>
<td>Reduce both bolus and infusion by 25%</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Discontinue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Platelets < 75 x 10^9/L
OR Grade 3-4 thrombocytopenia

Non-haematological toxicities

Renal Impairment
Calculate creatinine clearance using Cockcroft and Gault. If borderline, an EDTA should be requested.

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Oxaliplatin</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 30ml/min</td>
<td>Give 100% dose</td>
<td>Give 100% dose</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>&lt; 30ml/min</td>
<td>Omit</td>
<td>Give 50% dose</td>
<td>Give 80% dose</td>
</tr>
</tbody>
</table>

Hepatic Impairment

<table>
<thead>
<tr>
<th>Liver Function</th>
<th>Oxaliplatin</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin 1.5 – 3 x ULN or ALP &gt; 5 x ULN</td>
<td>Give 100% dose</td>
<td>Give 50% dose</td>
<td>Give 100% dose</td>
</tr>
<tr>
<td>*Bilirubin &gt; 3x ULN</td>
<td>Give 50% dose</td>
<td>Omit</td>
<td>Give 100% dose</td>
</tr>
</tbody>
</table>

* The clearance of irinotecan is decreased in patients with hyperbilirubinemia and prothrombin time greater than 50%. Weekly monitoring of complete blood counts is recommended in this patient population.

* Note that significantly impaired hepatic function may be a sign of disease progression and may require cessation of, or change in treatment. Always discuss deteriorating organ function with consultant.
Dose modifications for other toxicities

Diarrhoea & fever

*Note that severe diarrhoea and/or severe mucositis early in the first treatment cycle can be the first presenting toxicity due to DPD enzyme deficiency, in which case potentially fatal neutropenia can quickly follow.*

<table>
<thead>
<tr>
<th>Grade 3-4 diarrhoea OR diarrhoea &amp; fever</th>
<th>Immediate action</th>
<th>Oxaliplatin</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Give 100% dose</td>
<td>Reduce to 150mg/m²</td>
<td>Omit 5FU bolus</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Reduce to 60mg/m²</td>
<td>Maintain 150mg/m² dose</td>
<td>Omit 5FU bolus and reduce infusion by 25%</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Discontinue</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Palmar-Plantar Erythema or mucositis

<table>
<thead>
<tr>
<th>Palmar-Plantar Erythema OR mucositis</th>
<th>Immediate action</th>
<th>Flurouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Give 75% dose</td>
</tr>
<tr>
<td>2nd appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>3rd appearance</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st appearance</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Give 50% dose</td>
</tr>
<tr>
<td>2nd appearance</td>
<td>Discontinue OR at consultants discretion, interrupt until resolved to grade 0-1 and give 50% dose</td>
<td></td>
</tr>
</tbody>
</table>

Paraesthesia

Cumulative dose related peripheral sensory neuropathy usually occurs after a cumulative oxaliplatin dose of 800mg/m². It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approx 3 – 5 months to recovery.

<table>
<thead>
<tr>
<th>Paraesthesia</th>
<th>Immediate action</th>
<th>Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 of any duration OR grade 2 paraesthesia lasting &gt;7 days</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Maintain 100% dose</td>
</tr>
<tr>
<td>Grade 2 paraesthesia persisting until next cycle</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Reduce to 60mg/m²</td>
</tr>
<tr>
<td>Grade 3 paraesthesia lasting &gt;7 days</td>
<td>Interrupt until resolved to grade 0-1</td>
<td>Reduce to 60mg/m²</td>
</tr>
<tr>
<td>Grade 3 paraesthesia persisting until next cycle OR Grade 4 of any duration</td>
<td>Discontinue oxaliplatin permanently</td>
<td></td>
</tr>
</tbody>
</table>
Comments:

Diarrhoea
Diarrhoea may occur within 30 – 90 minutes of irinotecan infusion, or may be delayed. Once a liquid stool occurs, loperamide 4mg should be taken immediately, followed by 2mg every 2 hours until diarrhoea-free for at least 12 hours. In no instance should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. Patients should be instructed to drink large volumes of water/electrolytes.

If diarrhoea persists for 24 hours despite loperamide, a prophylactic course of ciprofloxacin PO 250mg BD for 5 days should be started. Counsel the patient to call for advice. After 48 hours of persistent diarrhoea, the patient should be hospitalised for parenteral support and review of treatment.

Concomitant fever or vomiting will require hospitalisation for IV hydration.

**Loperamide and ciprofloxacin must be dispensed to patients on discharge, and counselled to ensure they know how and when to use them.**

Allergic reaction to oxaliplatin
Immediate intervention is to stop the infusion and seek medical help. Treat with IV corticosteroid and antihistamine. After full recovery, the patient may continue with folinic acid and 5FU.

At consultant discretion, the patient may be re-challenged with oxaliplatin at the next cycle, start infusion slowly and increase rate as tolerated. Prescribe the following premedication:

Dexamethasone 4mg PO 6hrly x 3 doses, starting 24 hours pre-treatment, plus dexamethasone 8mg IV, chlorphenamine 10mg IV and ranitidine 50mg IV 30 minutes pre-dose.

*Patients who have severe reactions should not be re-challenged.*

Cholinergic syndrome
Cholinergic syndrome (diarrhoea, sweating, salivation, bradycardia) can be controlled by giving atropine 300micrograms subcutaneously at start of irinotecan administration. Should the syndrome develop, a further dose of atropine may be given and prophylactic atropine is recommended to be given in subsequent cycles.

Coronary artery spasm
Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management & prognosis is not particularly strong. The incidence is estimated to be between 2% and 18%. Coronary artery spasm is usually reversible on discontinuing treatment. Should a patient receiving 5FU present with chest pains, stop the treatment. Standard investigation and treatment of angina may be required. If re-challenge is deemed necessary, this can be performed under close supervision, but should symptoms redevelop, 5FU should be withdrawn permanently. Discuss with consultant.

Acute Cold-related Dysaesthesia & Laryngopharyngeal dysaesthesia (Oxaliplatin)
Many patients experience transient paraesthesia of hands & feet, some patients experience laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion, and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patient should be advised on precautions to be taken. Does not require treatment or dose reduction.

After an episode of **laryngopharyngeal dysesthesia**, subsequent infusions of oxaliplatin should be given **over 6 hours**. Consider infusion of calcium gluconate 1g (10ml of 10% solution) and magnesium sulphate 1g (2ml of 50% solution) in 100ml Glucose 5% before and after oxaliplatin chemotherapy.
Clinical symptoms | Laryngopharyngeal dysaesthesia | Platinum hypersensitivity
---|---|---
Dyspnoea | Present | Present
Bronchospasm | Absent | Present
Laryngospasm | Absent | Present
Anxiety | Present | Present
O2 saturation | Normal | Decreased
Difficulty swallowing | Present (loss of sensation) | Absent
Pruritus | Absent | Present
Cold induced symptoms | Yes | No
Blood pressure | Normal or increased | Normal or decreased

**Treatment**
- Anxiolytics; observation in a controlled clinical setting until symptoms abate or at clinician’s discretion. Subsequent infusions of oxaliplatin should be given over 6 hours.
- Oxygen, steroids, adrenaline bronchodilators, antihistamine, fluids and vasopressors if appropriate.

**Pulmonary fibrosis**
Oxaliplatin therapy should be interrupted if symptoms indicative of pulmonary fibrosis develop – non-productive cough, dyspnoea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.

**Hemolytic Uremic Syndrome (HUS)**
Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is <25%, platelets <100,000 and creatinine >135 umol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

**Venous Occlusive Disease**
Venous Occlusive Disease is a rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or haematemesis immediately.

**Drug interactions:**
- **Irinotecan**
  - Strong inhibitors (e.g. ketoconazole) or inducers (e.g. rifampicin, carbamazepine, phenytoin, phenobarbital, St John’s Wort) of CYP3A4 may alter metabolism of irinotecan
  - Aprepitant- increases irinotecan plasma levels
  - Citalopram- increased risk of myopathy or rhabdomyolysis
  - Lopinavir/ritonavir – reduced clearance of irinotecan
- **5FU**
  - Metronidazole - increased plasma levels of 5FU
  - Allopurinol- reduced efficacy of 5FU
  - Folinic acid – increase 5FU toxicity
  - Phenytoin – increases phenytoin levels, risk of toxicity
  - Hydrochlorthiazide – risk of myelosuppression
  - Coumarin anticoagulants - monitor INR, increased risk of bleeding
Oxaliplatin  Aminoglycoside antibiotics- increased risk of ototoxicity with oxaliplatin

Avoid live vaccines

References:
UCLH – Dosage adjustment for cytotoxics in renal impairment. Jan 2009
UCLH – Dosage adjustment for cytotoxics in hepatic impairment. Jan 2009