FOLFIRINOX
Metastatic Adenocarcinoma of the Pancreas

**Background:** FOLFIRINOX has a 4.3 month overall survival advantage compared with single-agent gemcitabine in patients with metastatic adenocarcinoma of the pancreas. It is now accepted as a standard of care for the 1st line treatment of patients with good performance status.

**Patient Group:**
Metastatic adenocarcinoma of the pancreas suitable for combination chemotherapy.
No previous chemotherapy for metastatic disease.
PS - ECOG 0 or 1
Creatinine clearance ≥ 30 mL/min
Bilirubin ≤ 1.5 x ULN

**Pre-treatment Assessment:**
Clinical assessment
Performance score
Weight, FBC, U&E, LFTs and Creatinine clearance
CT Scan and histology

**Treatment Threshold**
Haemoglobin > 10g/dl
WCC > 3 x 10^9/L
ANC ≥ 1.5 x 10^9/L
Platelets ≥ 100 x10^9/L
Creatinine clearance ≥ 30 mL/min

**Pre-Medication:**
Administered 30-60minutes prior to chemotherapy:
Dexamethasone 8mg IV bolus over 3-5 minutes or PO
Ondansetron 8mg IV bolus over 3-5 minutes or PO
Regimen Details:

Day 1

**Oxaliplatin** 85mg/m² IV in 500mL glucose 5%. Administered over 2 hours.

**Folinic Acid** 350mg IV in 250mL glucose 5%. Administered over 2 hour.

**Atropine Sulphate** 0.24mg injected SC

**Irinotecan** 180mg/m2 IV in 250mL sodium chloride 0.9% Administered over 30-90 minutes

**Fluorouracil** 400mg/m² IV bolus over 3-5 minutes

**Fluorouracil** 2400mg/m² IV infused over 46 hours via ambulatory infusor.

Treatment is repeated every 14 days for up to 13 cycles.

Administration:

- A PICC line is required for the ambulatory infusion pump
- Coronary artery spasm is a recognised complication of 5FU although the evidence base regarding aetiology, management and prognosis is not particularly strong. Coronary artery spasm is more common in patients receiving continuous infusions of 5FU, and is usually reversible on discontinuing the infusion. Should a patient receiving 5FU present with chest pains, stop the 5FU. Standard investigation and treatment of angina may be required
- A glucose 5% flush should be administered before and after the oxaliplatin
**Oxaliplatin Infusion**

- **Laryngo-pharyngeal dysesthesia** is an unusual dysesthesia characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician’s discretion. In subsequent cycles, the duration of infusion should be over 6 hours.

- **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. The infusion should be stopped immediately and the protocol for managing hypersensitivity reactions followed.

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Laryngo-pharyngeal dysesthesia</th>
<th>Platinum Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>O2 saturation</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>Present (loss of sensation)</td>
<td>Absent</td>
</tr>
<tr>
<td>Pruritus</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cold induced symptoms</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normal or increased</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>Treatment</td>
<td>Anxiolytics, observation, and reassurance until symptoms abate.</td>
<td>Oxygen, steroids, chlorphenamine, adrenaline, bronchodilators.</td>
</tr>
</tbody>
</table>

**Anti-emetics:** Highly emetic

**Additional Medication:**
Ciprofloxacin 500mg BD for 7/7 to be taken after seeking medical advice, supplied with the first cycle.
Loperamide 2mg every two hours once first liquid stool appears and continue until 12 hours after the last liquid stool. Do not use for longer than 48 hours supplied with first cycle and as necessary.

**Monitoring and Assessment:**
Clinical assessment – medical review prior to each cycle
FBC U&E, LFT– prior to each cycle
CT scan: after cycle 5, 9 and 13 or to confirm disease progression.
Dose Modifications:

**Haematological Toxicity**

Do not start new cycle until platelets $\geq 100 \times 10^9$/L and ANC $\geq 1.5 \times 10^9$/L, recovery from diarrhoea (without loperamide for at least 24 hours), and other non-hematologic toxicities have recovered to $\leq$ grade 2.

If the ANC is less than $1.5 \times 10^9$/L on Day 1, or if the patient has experienced, febrile neutropenia or a grade 3/4 infection or grade 4 neutropenia then defer treatment until recovery and follow the table below for dose modification.

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>5FU</th>
<th>Irinotecan</th>
<th>Oxaliplatn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>Omit bolus dose</td>
<td>150mg/m²</td>
<td>Full dose</td>
</tr>
<tr>
<td>2nd</td>
<td>Omit bolus dose</td>
<td>150mg/m²</td>
<td>65mg/m²</td>
</tr>
<tr>
<td>3rd</td>
<td>Stop treatment</td>
<td>Stop treatment</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>

If the platelets are less than $100 \times 10^9$/L on Day 1 or if there has been grade 3/4 thrombocytopenia since the previous cycle defer treatment until recovery and follow the dose modifications in the table below.

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>5FU</th>
<th>Irinotecan</th>
<th>Oxaliplatn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>75%</td>
<td>Full dose</td>
<td>65mg/m²</td>
</tr>
<tr>
<td>2nd</td>
<td>75%</td>
<td>150mg/m²</td>
<td>65mg/m²</td>
</tr>
<tr>
<td>3rd</td>
<td>Stop treatment</td>
<td>Stop treatment</td>
<td>Stop treatment</td>
</tr>
</tbody>
</table>
**Non-Haematological Toxicity**

For all other non-haematological NCI-CTC grade 3 and above toxicities - delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced (fluorouracil to 75% of the original dose, irinotecan to 150mg/m², oxaliplatin to 65mg/m²) or discontinued as appropriate. The following guidance applies in specific cases.

**Diarrhoea**

If diarrhoea from the previous cycle, even if not severe, has not resolved (without loperamide for at least 24 hours) by the time the next cycle is due, delay treatment by 1 week. Follow the table below for dose reductions in subsequent cycles:

<table>
<thead>
<tr>
<th>Diarrhoea</th>
<th>Irinotecan</th>
<th>Oxaliplatin</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence of Grade 3 or 4</td>
<td>150mg/m²</td>
<td>Full dose</td>
<td>Omit bolus dose</td>
</tr>
<tr>
<td>diarrhoea or diarrhoea + fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>150mg/m²</td>
<td>65mg/m²</td>
<td>Omit bolus dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and reduce dose of infusion to 75%</td>
<td></td>
</tr>
<tr>
<td>3rd occurrence</td>
<td></td>
<td>Stop treatment</td>
<td></td>
</tr>
</tbody>
</table>

Doses should not be re-escalated once they have been reduced for toxicity.

**Neurological Toxicity**

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:

- If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m².

- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m².

- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.

**Pulmonary Toxicity**

Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely with oxaliplatin. Supportive care is required. Oxaliplatin therapy should be interrupted if symptoms
indicative of pulmonary fibrosis develop: non-productive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.

Renal impairment

If creatinine clearance < 20mL/min omit Oxaliplatin
No dose reduction necessary for Irinotecan.
Dose reduction may be considered in severe renal impairment for Fluorouracil.

Hepatic impairment

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Irinotecan</th>
<th>Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5 x ULN</td>
<td>Full dose</td>
<td>Full dose</td>
</tr>
<tr>
<td>1.5 - 4 X ULN</td>
<td>Clinical decision</td>
<td>Dose reduction by a third or half at clinician's discretion</td>
</tr>
<tr>
<td>&gt; 4 x ULN</td>
<td>Omit</td>
<td>Omit</td>
</tr>
</tbody>
</table>

Pharmaceutical Care:

- Counsel patients to avoid cold drinks and exposure to cold air, especially on day of oxaliplatin.

- Potential Drug Interactions: Anticonvulsants and other drugs which induce Cytochrome P450 3A4 isoenzyme activity e.g. Carbamazepine, Phenytin and St John’s Wort may decrease the therapeutic and toxic effects of irinotecan. Fluorouracil interactions with warfarin and phenytin may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping fluorouracil).

Most Common Toxicities:

- Myelosuppression ± infection, bleeding (may be severe)
- Neuropathy (may be severe)
- Nausea and or vomiting
- Fatigue
- Abdominal pain
- Alopecia
- ↑ LFTs
• Diarrhoea
• Anorexia
• Mucositis
• Constipation
• Oedema
• Eye disorders
• Photosensitivity
• Rash
• Handfoot syndrome
• Hypersensitivity

References:
