**NCCP Chemotherapy Regimen**

**Modified FOLFOX-6 Chemoradiation Therapy-14 day**

**INDICATIONS FOR USE:**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>*Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive squamous cell carcinoma (SCC) or adenocarcinoma of the oesophagus in combination in patients for whom a CIplatin based regimen is contraindicated.</td>
<td>C15</td>
<td>00509a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined the indication has yet to be assessed through the formal HSE reimbursement process*

**TREATMENT:**

*The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.*

Chemotherapy is administered every 14 days for six cycles according to the treatment table below unless disease progression or unacceptable toxicity develops. The first three cycles (week 1-6) are administered concurrently with radiotherapy (week 1-6) and the final three cycles are given after radiotherapy.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Oxaliplatin</td>
<td>85mg/m²</td>
<td>IV infusion</td>
<td>500ml glucose 5% over 2hrs</td>
<td>Every 14 days</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Folinic Acid (Calcium leucovorin)</td>
<td>200mg/m²</td>
<td>IV infusion</td>
<td>250ml glucose 5% over 2hrs</td>
<td>Every 14 days</td>
</tr>
</tbody>
</table>

Flush line with glucose 5% before administering 5-FU

| 3              | 1   | 5-Fluorouracil           | 400mg/m²   | IV BOLUS   |                | Every 14 days |
| 4              | 1   | 5-Fluorouracil           | 1600mg/m²  | Continuous IV infusion | Over 46h in 0.9% NaCl. | Every 14 days |

Oxaliplatin is incompatible with 0.9% NaCl. For oxaliplatin doses ≤ 104mg use 250ml glucose 5%.

Oxaliplatin administration must always precede the administration of 5-Fluorouracil.

Oxaliplatin may be given at the same time as Folinic Acid (Calcium Leucovorin) using a Y connector.

Acute neurotoxicity is common with oxaliplatin and can be precipitated on exposure to the cold therefore in this regimen patients should NOT suck on ice chips during the bolus injection of fluorouracil.
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ELIGIBILITY:
- Indications as above
- ECOG 0-2
- Adequate haematological, renal and liver status

CAUTION:
Use with caution in patients with
- Previous pelvic radiotherapy
- Recent MI
- Uncontrolled angina, hypertension, cardiac arrhythmias, CHF
- In patients with baseline greater than 3 loose bowel movements (BM) per day (in patients without colostomy or ileostomy)
- Symptomatic peripheral neuropathy

EXCLUSIONS:
- Hypersensitivity to oxaliplatin or any of the excipients
- Severe renal impairment (creatinine clearance < 30ml/min)
- Breast feeding
- Peripheral neuropathy with functional impairment prior to first cycle

PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:
Baseline tests:
- Blood, liver and renal profile
- ECG (if patient has compromised cardiac function)

Regular tests:
- Blood, liver and renal profile prior to each cycle
- Evaluate for peripheral neuropathy every 2 cycles

Disease monitoring:
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:
- Any dose modification should be discussed with a Consultant
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Haematological:

Table 1: Dose Modifications for Haematological Toxicity

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 and ≥ 75</td>
<td></td>
<td>100% Dose</td>
</tr>
<tr>
<td>&lt; 1.5 and/or &lt; 75</td>
<td></td>
<td>Delay chemotherapy until recovery</td>
</tr>
<tr>
<td>&lt; 1 and/or &lt; 50</td>
<td></td>
<td>Delay chemotherapy until recovery. Omit bolus 5-fluorouracil and reduce dose of oxaliplatin to 65mg/m² for subsequent cycles</td>
</tr>
</tbody>
</table>

Febrile neutropenia

Renal and Hepatic Impairment:

Table 2: Recommended dose modifications in patients with renal or hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>CrCl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td>&gt;20</td>
<td>Treat at normal dose and monitor renal function</td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>Dose reduce</td>
<td></td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td></td>
</tr>
</tbody>
</table>

Little information available. Probably no dose reduction necessary Clinical decision

<table>
<thead>
<tr>
<th>Bilirubin (micromol/L)</th>
<th>AST</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 85</td>
<td>&lt; 180</td>
<td>100%</td>
</tr>
<tr>
<td>&gt; 85 or &gt; 180</td>
<td></td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity
Management of adverse events:

Table 3: Dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
</table>
| *Peripheral neuropathy*  
  Grade 2  
  • Persistent between cycles  
  Grade 3  
  • Duration >7 and <14 days  
  • Persistent between cycles  
  Grade 4  
  • Duration >14 days | Reduce oxaliplatin to 65mg/m²  
  Reduce oxaliplatin to 65mg/m²  
  Discontinue oxaliplatin  
  Discontinue oxaliplatin  |
| Laryngo-pharyngeal dysaesthesia  
  Grade 3 | Increase infusion time from 2 to 6 hrs  |
| Stomatitis or Diarrhoea  
  Grade 4 | Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows:  
  1⁰ occurrence: Cease bolus fluorouracil  
  2⁰ occurrence: Reduce oxaliplatin to 65mg/m² and infusional fluorouracil to 1200mg/m²  
  3⁰ occurrence: Cease treatment  |
| Unexplained respiratory symptoms e.g. Non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates | Discontinue oxaliplatin until interstitial disease or pulmonary fibrosis excluded.  |

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate (Refer to local policy).

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity.

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment (Refer to local policy).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- Laryngopharyngeal dysesthesia: An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
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- **Gastrointestinal toxicity:** Patients treated with fluorouracil should be closely monitored for diarrhea and managed appropriately.
- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with fluorouracil, should be carefully monitored during therapy.
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Rare, life-threatening toxicities such as stomatitis, mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.
- **Platinum Hypersensitivity:** Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Extravasation:** Oxaliplatin causes irritation if extravasated (Refer to local policy).
- **Venous occlusive disease:** A rare but serious complications 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 hematemesis immediately.
- **Haemolytic Uremic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.
- **Palmar Plantar Erythrodysesthesia (PPE):** This has been reported as an unusual complication of high dose bolus or protracted continuous therapy with fluorouracil.

**DRUG INTERACTIONS:**
- Marked elevations of prothrombin time and INR have been reported in patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin
- Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydroprimidine dehydrogenase activity
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**
- Oxaliplatin - L01XA03
- 5-Fluorouracil - L01BC02
- Folinic acid - V03AF03

**REFERENCES:**


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The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician, and is subject to HSE’s terms of use available at http://www.hse.ie/eng/Disclaimer.

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