**CISplatin 75mg/m² and 5-Fluorouracil Chemoradiation Therapy- Herskovic Regimen**

**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>Locally advanced squamous or adenocarcinoma of the oesophagus not suitable for surgery</td>
<td>C15</td>
<td>00460a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If 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 on weeks 1, 5, 8 and 11* with CISplatin being administered on Day 1 and 5-fluorouracil (5-FU) being administered by continuous infusion on Days 1-4. Radiotherapy is administered concurrently with chemotherapy* during weeks 1-5.

*unless disease progression or unacceptable toxicity develops.

<table>
<thead>
<tr>
<th>Order of Admin</th>
<th>Week</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1, 5</td>
<td>1</td>
<td>*CISplatin</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>1000ml NaCl 0.9% over 2 hours</td>
<td>Concurrently with radiotherapy (week 1-5)</td>
</tr>
<tr>
<td>2</td>
<td>1, 5</td>
<td>1-4</td>
<td>5-Fluorouracil</td>
<td>1000mg/m²/day</td>
<td>Continuous IV infusion over 4 days</td>
<td>Infusor pump</td>
<td>Concurrently with radiotherapy (week 1-5)</td>
</tr>
<tr>
<td>1</td>
<td>8, 11</td>
<td>1</td>
<td>*CISplatin</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>1000ml NaCl 0.9% over 2 hours</td>
<td></td>
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<td>2</td>
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<td>Infusor pump</td>
<td></td>
</tr>
</tbody>
</table>

*Pre and post hydration therapy required for CISplatin

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate (MgSO₄) ([+/-KCl 20mmol/L if indicated] in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above

Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (3, 4).
ELIGIBILITY:
- Indications as above
- ECOG status 0-2

EXCLUSIONS:
- Hypersensitivity to CISplatin, 5-fluorouracil or any of the excipients
- Pregnancy
- Breast Feeding
- Creatinine Clearance < 60ml/min

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

TESTS:
Baseline tests:
- FBC, renal and liver profile
- Audiometry and creatinine clearance as clinically indicated

Regular tests:
- FBC, renal and liver profile

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

Haematological:

<table>
<thead>
<tr>
<th>ANC (x 10^9/L) (on day of chemotherapy)</th>
<th>Platelets (x 10^9/L) (at any stage during cycle)</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1</td>
<td>≥100</td>
<td>100% Dose</td>
</tr>
<tr>
<td>0.5 – 0.99</td>
<td>50 – 99</td>
<td>Delay treatment until recovery</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>&lt;50</td>
<td>Delay treatment until recovery and consider reducing CISplatin and 5-fluorouracil by 25% for subsequent cycles</td>
</tr>
</tbody>
</table>

Febrile neutropenia

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Renal and Hepatic Impairment:

Table 2: Dose Modification for in Renal and Hepatic Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISplatin</td>
<td>Cr Cl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>45-59</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt;45</td>
<td>Consider CARBOplatin-Clinical decision</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.</td>
</tr>
</tbody>
</table>

Table 3: Dose Modifications for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 Diarrhoea or Stomatitis</td>
<td>Delay treatment until toxicity has resolved to grade ≤ 1 and then treatment may be resumed with a 25% reduction in the dose of 5-fluorouracil.</td>
</tr>
<tr>
<td>Grade ≥ 2 peripheral neuropathy</td>
<td>Omit CISplatin</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
CISplatin High (Refer to local policy).
5-Fluorouracil Low (Refer to local policy)

PREMEDICATIONS:
Pre and Post Hydration therapy required for CISplatin administration (Reference local policy or see recommendations above).

OTHER SUPPORTIVE CARE:
Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS
This medicinal product is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details

- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
- **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

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Tumour Group: Gastrointestinal
NCCP Regimen Code: 00460
ISMO Contributor: Prof Maccon Keane

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fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.

**DRUG INTERACTIONS:**

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- 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:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ATC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CISplatin</td>
<td>L01XA01</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>L01BC02</td>
</tr>
</tbody>
</table>

**REFERENCES:**


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