CISplatin and 5-Fluorouracil Therapy-28 day cycle

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 or metastatic head and neck cancer</td>
<td>C76</td>
<td>00314a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

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.

CISplatin and 5-Fluorouracil are administered on days 1-4 of a 28 day cycle until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered on Day 1.

<table>
<thead>
<tr>
<th>Admin. Order</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route and Method of Administration</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-4</td>
<td>CISplatin</td>
<td>25mg/m²</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 2 hours</td>
<td>Every 28 days</td>
</tr>
<tr>
<td>2</td>
<td>1-4</td>
<td>5-Fluorouracil</td>
<td>1000mg/m²/ day</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 22 hours</td>
<td>Every 28 days</td>
</tr>
</tbody>
</table>

*Pre hydration therapy required for CISplatin

See local hospital policy recommendations.

Suggested pre-hydration 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

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate organ function; ANC > 1.5 x10⁹ cells/L, platelets 100 x10⁹/L serum creatinine ≤ 1.5 x ULN, transaminases ≤5 x ULN, bilirubin ≤1.5 x ULN

EXCLUSIONS:

- Hypersensitivity to CISplatin, 5-fluorouracil or any of the excipients
- Pregnancy
- Lactation
- Pre existing neuropathies ≥ grade 2
- Severe liver impairment
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus
- Fluorouracil should not be given to patients who are known to be homozygotic for dihydropyrimidine dehydrogenase (DPD) or with known complete absence of DPD activity
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PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:
Baseline tests:
- FBC, Renal and liver profile
- ECG (if patient has compromised cardiac function).
- Audiology and creatinine clearance if clinically indicated

Regular tests:
- FBC, Renal and liver profile before each cycle

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 of 5-Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 1.5</td>
<td>or 75-100</td>
<td>750mg/m^2/day x 4 days</td>
</tr>
<tr>
<td>&lt;1</td>
<td>or &lt;75</td>
<td>375mg/m^2/day x 4 days</td>
</tr>
</tbody>
</table>

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></td>
<td>No dose reduction necessary</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>45-59</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>Clinical decision. Consider using CARBOplatin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5-Fluorouracil</th>
<th>Consider dose reduction in severe renal impairment only</th>
<th>Bilirubin</th>
<th>AST</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;85</td>
<td>&lt;180</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;85 or &gt;180</td>
<td>Contra-indicated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.
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Non-haematological toxicity

Table 3: Dose modification schedule for CISplatin based on adverse events

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 2 peripheral neuropathy</td>
<td>Omit CISplatin and consider substituting CISplatin with CARBOplatin</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (Refer to local policy).

PREMEDICATIONS: Hydration prior CISplatin administration (Reference local policy or see recommendations above).

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **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 fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation prior to continuing with treatment.

DRUG INTERACTIONS:

- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary, monitor renal function closely.
- 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 dihydropyrimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CISplatin - L01XA01
5-Fluorouracil - L01BC02

NCCP Regimen: CISplatin and 5-Fluorouracil Therapy
Published: 03/05/2016
Review: 13/05/2025
Version number: 3

Tumour Group: Head & Neck
NCCP Regimen Code: 00314
ISM0 Contributor: Prof Maccon Keane

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens
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REFERENCES:


<table>
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<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/05/2016</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>2/05/2018</td>
<td>Applied new NCCP regimen template. Updated treatment table, revised Cisplatin hydration regimen recommendations and standardised dosing in renal and hepatic impairment.</td>
<td>Prof Maccon Keane</td>
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<td>3</td>
<td>13/05/2020</td>
<td>Exclusion criteria updated</td>
<td>Prof Maccon Keane</td>
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.