CISplatin and 5-Fluorouracil Therapy-28 day cycle

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally advanced or metastatic head and neck cancer	C76	00314a	Hospital

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 patients 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.

Admin. Order	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	1-4	[a]CISplatin	25mg/m^2	IV infusion	1000ml 0.9% NaCl over 2 hours	Every 28 days
2	1-4	5-Fluorouracil	1000mg/m^2/ day	IV infusion	1000ml 0.9% NaCl over 22 hours	Every 28 days

[a]Pre hydration therapy required for CISplatin

See local hospital policy recommendations.

Suggested pre-hydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) (+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above

ELIGIBILTY:

- Indications as above
- ECOG status 0-2
- Adequate organ function; ANC > 1.5 x10^9 cells/L, platelets 100 x10^9/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

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 1: Dose modification for haematological toxicity

ANC (x 10^9/L) (on day of chemotherapy)		Platelets (x 10^9/L) (at any stage during cycle)	Dose of 5-Fluorouracil
1 -1.5	or	75-100	750mg/m^2/day x 4 days
<1	or	<75	375mg/m^2/day x 4 days

Renal and Hepatic Impairment:

Table 2: Dose modification for renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td rowspan="4">CISplatin</td><td>GFR (ml/min)</td><td>Dose</td><td colspan="4" rowspan="4">No dose reduction necessary</td></tr>
<tr><td>≥60</td><td>100%</td></tr>
<tr><td>45-59</td><td>75%</td></tr>
<tr><td><45</td><td>Clinical decision.
Consider using CARBOplatin</td></tr>
<tr><td>5-Fluorouracil</td><td colspan="2" rowspan="3">Consider dose reduction in severe renal impairment only</td><td>Bilirubin</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>Contra-indicated</td></tr>
<tr><td colspan="4">Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.</td></tr>
</table>

Non-haematological toxicity

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

Adverse reaction	Recommended dose modification
Grade ≥ 2 peripheral neuropathy	Omit CISplatin and consider substituting CISplatin with CARBOplatin

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 dihydroprimidine dehydrogenase activity.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CISplatin - L01XA01
5-Fluorouracil - L01BC02

REFERENCES:

1. Forastiere AA, Metch B, Schuller DE, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: A Southwest Oncology Study. J Clin Oncol, 1992; 10: 1245-1251
2. BCCA Protocol Summary for Advanced Nasopharyngeal Cancer of the Head and Neck using Platinum and Fluorouracil HNNAVFUP Revised October 2013
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting V2 2019. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Cisplatin 1mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed May 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-081-001_13022020153905.pdf
5. Fluorouracil 50mg/ml Solution for injection or Infusion Summary of Product Characteristics Accessed May 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_10052019144741.pdf

Version	Date	Amendment	Approved By
1	3/05/2016		Prof Maccon Keane
2	2/05/2018	Applied new NCCP regimen template. Updated treatment table, revised CISplatin hydration regimen recommendations and standardised dosing in renal and hepatic impairment.	Prof Maccon Keane
3	13/05/2020	Exclusion criteria updated	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.