CISplatin, 5-Fluorouracil and Radiation Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of anal canal carcinoma	C21	00594a	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 is administered at a dose of 60mg/m^2 on day 1 and 29.

5-Fluorouracil is administered at a dose of 1000mg/m^2/day on days 1-4 (week 1) and 29-32 (week 5) by continuous 24 h intravenous infusion with radiotherapy.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate
1	1,29	CISplatin [a]	60mg/m^2	IV Infusion	1000ml 0.9% NaCl over 2 hours
2	1-4 29-32	5-Fluorouracil[b]	1000mg/m^2/day (Total dose= 4000mg/m^2 over 96 hours)	IV infusion	Continuous IV infusion over 4 days
[a]Pre and Post hydration therapy required. See local hospital policy for recommendations. Suggested Pre-hydration for CISplatin 1. Administer 10mmol magnesium sulphate ($MgSO_4$) (+/-KCl 10-20mmol/L if indicated) in 1000ml sodium chloride 0.9% over 60 minutes Administer CISplatin as described above Post hydration: Administer 1000ml 0.9% NaCl over 60 minutes Mannitol 10% may be used 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[2, 3].					
[b]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency					

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate hepatic, renal and bone marrow function

EXCLUSIONS:

- Hypersensitivity to CISplatin, 5-Fluorouracil, or any of the excipients
- CISplatin
    - Pre-existing neuropathies ≥ grade 2
    - Creatinine clearance < 60ml/min
    - Significant hearing impairment/tinnitus
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency
- Pregnancy
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile weekly throughout treatment

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:

- Consider a reduced starting dose in patients with identified partial DPD deficiency
    - Initial dose reduction may impact the efficacy of treatment
    - In the absence of serious toxicity, subsequent doses may be increased with careful monitoring
- Any dose modification should be discussed with a Consultant

Haematological:

Table 1: Dose modification in haematological toxicity

ANC (x10^9/L)		Platelets (x10^9/L)	Dose
>1	And	≥100	100%
0.5- 0.99	Or	50-99	Delay treatment until recovery
<0.5	Or	<50	Delay treatment until recovery and consider reducing CISplatin and 5-Fluorouracil by 25% for subsequent cycles
Febrile neutropenia			

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

<table>
<tr><th colspan="3">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td rowspan="4">CISplatin</td><td>CrCl (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>Hold CISplatin or delay with additional fluids</td></tr>
<tr><td rowspan="4">5-Fluorouracil</td><td colspan="2" rowspan="4">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>Or</td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td></td><td>>180</td><td>Contraindicated</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. Increase dose if no toxicity.</td></tr>
</table>

Management of adverse events:

Table 3: Dose Modification schedule based on Adverse Events

Adverse reactions	Recommended dose modification
Diarrhoea or Mucositis	
Grade 2	Delay treatment with 5-Fluorouracil until toxicity has resolved to Grade 1 or less
Grade ≥ 3	Delay treatment until toxicity has resolved to Grade 1 or less and reduce 5-Fluorouracil by 50% for subsequent cycles
Peripheral neuropathy	
Grade 2	Reduce dose of CISplatin by 25% or consider alternative therapy
Grade 3	Omit CISplatin and consider alternative therapy

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

PREMEDICATIONS: Hydration pre and post CISplatin administration **(Reference local policy or see recommendations above)**.

OTHER SUPPORTIVE CARE:

- Anti-diarrhoeal treatment (**Refer to local policy).**
- Mouth Care (**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.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately. Avoid aminoglycoside antibiotics.
- **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Strongly encourage oral hydration. If oral hydration is not possible (e.g. excessive nausea), IV hydration is indicated. Avoid nephrotoxic drugs such as aminoglycoside antibiotics where possible. Where treatment with nephrotoxic drugs must be used, monitor renal function.
- **Ototoxicity and sensory neural damage**: These are associated with CISplatin. They should be assessed by history prior to each cycle.
- **Hypersensitivity**: Hypersensitivity reactions have been reported with CISplatin.
- **Myocardial ischaemia and angina**: Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.
- **DPD deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE), HFS has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-Fluorouracil.

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 5-Fluorouracil regimens.
- Concurrent administration of CISplatin and phenytoin may result in decreased serum levels of phenytoin. In these patients, monitor plasma levels of phenytoin and dose adjust accordingly.

- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 5-fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil metabolizing enzyme DPD
- Caution should be taken when using 5-Fluorouracil in conjunction with medications which may affect DPD.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1	25/02/2020		Prof Maccon Keane
2	3/9/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane
3	10/03/2021	Reviewed. Amended treatment table (CISplatin pre-hydration)	Prof Maccon Keane
3a	23/11/2023	Formatting changes and grammatical corrections.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.