NCCP Chemotherapy Regimen

Neoadjuvant DOCEtaxel, CISplatin, 5-Fluorouracil and Chemoradiation and Surgery

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>Induction treatment of patients with Stage III or IV non-metastatic squamous cell carcinoma of the head and neck</td>
<td>C76</td>
<td>00315a</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.

<table>
<thead>
<tr>
<th>Indication</th>
<th>DOCEtaxel and CISplatin are administered on day 1 and 5-Fluorouracil is administered on days 1-4 of a 21 day cycle for 3 cycles unless disease progression or unacceptable toxicity develops (Ref Treatment Table 1).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoradiation</td>
<td>CARBOplatin AUC 1.5 weekly concomitantly with radiotherapy for 7 weeks to start 3 to 8 weeks (day 22 to day 56) following start of third cycle of induction chemotherapy</td>
</tr>
<tr>
<td>Surgery</td>
<td>Considered 6-12 weeks following completion of chemoradiation</td>
</tr>
</tbody>
</table>

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

Table 1: Treatment Table for Induction Chemotherapy with DOCEtaxel, CISplatin and 5-Fluorouracil

<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</td>
<td>DOCEtaxel</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>250ml 0.9% sodium chloride over 60min</td>
<td>Every 21 days for 3 cycles</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>CISplatin</td>
<td>75mg/m²</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 2 hours</td>
<td>Every 21 days for 3 cycles</td>
</tr>
<tr>
<td>3</td>
<td>1-4</td>
<td>5-Fluorouracil</td>
<td>1000mg/m²</td>
<td>IV infusion</td>
<td>1000ml 0.9% NaCl over 22 hours</td>
<td>Every 21 days for 3 cycles</td>
</tr>
</tbody>
</table>

*For doses > 185mg use 500mL infusion bag. Use non-PVC equipment

*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 60 mins
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 (5, 6).

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ELIGIBILITY:
- Indications as above
- Life expectancy > 3 months
- ECOG status 0-1
- Adequate organ function; ANC > 1.5 x 10^9 cells/L, platelets 100 x 10^9/L
- Planned for definitive chemoradiation and surgery

EXCLUSIONS:
- Hypersensitivity to DOCEtaxel, CISplatin, 5-fluorouracil or any of the excipients
- Lactation
- Pre existing neuropathies ≥ grade 2
- Severe liver impairment
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Significant hearing impairment/tinnitus

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
  *See Adverse Effects/Regimen specific complications for guidelines regarding hepatic dysfunction with DOCTaxel

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 2: Dose modification for haematological toxicity

<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 and DOCTaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5</td>
<td>and ≥100</td>
<td>100%</td>
</tr>
<tr>
<td>1 - 1.49</td>
<td>or 75-100</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;1</td>
<td>or &lt;75</td>
<td>Delay</td>
</tr>
</tbody>
</table>

Consider decreasing to 75% if an episode of febrile neutropenia occurs with prior cycle of treatment.
• If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the DOCETaxel dose should be reduced from 75 to 60 mg/m².
• If subsequent episodes of complicated neutropenia occur the DOCETaxel dose should be reduced from 60 to 45 mg/m².
• In case of Grade 4 thrombocytopenia the DOCETaxel dose should be reduced from 75 to 60 mg/m².
• In the pivotal SCCHN studies patients who experienced complicated neutropenia (including prolonged neutropenia, febrile neutropenia, or infection), it was recommended to use G-CSF to provide prophylactic coverage (e.g. day 6-15) in all subsequent cycles.

Renal and Hepatic Impairment:

Table 3: Dose modification for renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOCETaxel</td>
<td>No recommended dose modifications</td>
<td>ALP &gt; 2.5 ULN and AST and/or ALT &gt; 1.5 ULN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 6 ULN and/or AST and ALT &gt; 3.5 ULN (AST and ALT) and Bilirubin &gt; ULN</td>
</tr>
<tr>
<td>CISplatin</td>
<td>GFR (ml/min) Dose</td>
<td>No dose reduction necessary</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>
<tr>
<td>5-Fluorouracil</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Bilirubin &lt;85 Or AST &gt;180 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85 Or &gt;180 Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2.</td>
</tr>
</tbody>
</table>

- ALP = Alkaline Phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase ULN = Upper Limit of Normal
Non-haematological toxicity

Table 4: Dose modification schedule based on adverse events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 diarrhoea</td>
<td>• Reduce 5-Fluorouracil dose by 20%</td>
</tr>
<tr>
<td>• 1st episode</td>
<td>• Reduce DOCEtaxel dose by 20%</td>
</tr>
<tr>
<td>• 2nd episode</td>
<td></td>
</tr>
<tr>
<td>Grade 4 diarrhoea</td>
<td>• Reduce DOCEtaxel and 5-Fluorouracil dose by 20%</td>
</tr>
<tr>
<td>• 1st episode</td>
<td>• Discontinue treatment</td>
</tr>
<tr>
<td>• 2nd episode</td>
<td></td>
</tr>
<tr>
<td>Grade 3 stomatitis/mucositis</td>
<td>• Reduce 5-Fluorouracil dose by 20%</td>
</tr>
<tr>
<td>• 1st episode</td>
<td>• Stop 5-Fluorouracil only, at all subsequent cycles</td>
</tr>
<tr>
<td>• 2nd episode</td>
<td>• Reduce DOCEtaxel dose by 20%</td>
</tr>
<tr>
<td>• 3rd episode</td>
<td></td>
</tr>
<tr>
<td>Grade 4 stomatitis/mucositis</td>
<td>• Stop 5-Fluorouracil only, at all subsequent cycles</td>
</tr>
<tr>
<td>• 1st episode</td>
<td>• Reduce DOCEtaxel dose by 20%.</td>
</tr>
<tr>
<td>• 2nd episode</td>
<td></td>
</tr>
<tr>
<td>Grade 3 skin reaction</td>
<td>Decrease dose of DOCEtaxel to 60mg/m²</td>
</tr>
<tr>
<td></td>
<td>If the patient continues to experience these reactions at 60mg/m², the treatment should be discontinued</td>
</tr>
<tr>
<td>Grade &gt;2 peripheral neuropathy</td>
<td>Decrease dose of DOCEtaxel to 60mg/m²</td>
</tr>
<tr>
<td></td>
<td>If the patient continues to experience these reactions at 60mg/m², the treatment should be discontinued</td>
</tr>
<tr>
<td></td>
<td>Consider dose reduction of CISplatin at discretion of prescribing consultant</td>
</tr>
<tr>
<td>Grade ≥ 2 PPE</td>
<td>Delay 5-Fluorouracil until recovery to Grade ≤ 1 and reduce subsequent doses of 5-Fluorouracil by 20%</td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

**EMETOGENIC POTENTIAL:** High (Refer to local policy).

**PREMEDICATIONS:**

**DOCEtaxel**
- Dexamethasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration unless contraindicated. Patient must receive minimum of 3 doses pre-treatment.
- *Consideration may be given, at the discretion of the prescribing consultant, to the use of a single dose of dexamethasone 20mg IV immediately before chemotherapy where patients have missed taking the oral premedication dexamethasone as recommended by the manufacturer (7,8)*

**CISplatin**
- Hydration prior and post CISplatin administration *(Reference local policy or see recommendations above).*
OTHER SUPPORTIVE CARE:
Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities. See comment above in dose modifications.

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**: Most frequent adverse reaction. Fever or other evidence of infection must be assessed promptly and treated appropriately. DOCEtaxel should be administered when the neutrophil count is > 1.5x10⁹ cells/L.

- **Neutropenic Enterocolitis**: A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCEtaxel in France (8). This is a known and rare side effect of DOCEtaxel which may affect up to one in 1,000 people.

- **Fluid Retention**: Dexamethasone premedication must be given to reduce the incidence and severity of fluid retention. It can also reduce the severity of the hypersensitivity reaction.

- **Hypersensitivity Reactions**: Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of DOCEtaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of DOCEtaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with DOCEtaxel.

- **Extravasation**: DOCEtaxel causes pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).

- **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction.

- **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:

- **Risk of drug interactions causing increased concentrations of DOCEtaxel with CYP3A inhibitors**. Patients should also be counselled with regard to consumption of grapefruit juice.

- **Risk of drug interactions causing decreased concentrations of DOCEtaxel with CYP3A inducers**.

- **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**
NCCP Chemotherapy Regimen

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:

- DOCEtaxel - L01CD02
- CISplatin - L01XA01
- 5-Fluorouracil - L01BC02

REFERENCES:

5. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3
   https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>03/05/18</td>
<td>Applied new NCCP regimen template Updated treatment table, revised CISplatin hydration regimen recommendations and standardised</td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

NCCP Regimen: Neoadjuvant DOCEtaxel, CISplatin and 5-Fluorouracil Therapy and Chemoradiation and Surgery

Tumour Group: Head & Neck
NCCP Regimen Code: 00315

ISM0 Contributor: Prof Maccon Keane

Published: 03/05/2016
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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at; http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/