**CISplatin, Methotrexate and vinBLAStine Therapy**

**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>Neoadjuvant treatment of muscle invasive transitional cell carcinoma (TCC) of the urothelium</td>
<td></td>
<td>C67</td>
<td>00337a</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.

Treatment is administered as described below every 21 days for a maximum of 3 cycles or until disease progression or unacceptable toxicity develops.

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

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,8</td>
<td><em>CISplatin</em></td>
<td>100mg/m²</td>
<td>IV infusion</td>
<td>500ml 0.9% NaCl over 120min</td>
<td>Every 21 days for up to 3 cycles</td>
</tr>
<tr>
<td>1,8</td>
<td>Methotrexate</td>
<td>30mg/m²</td>
<td>IV Bolus</td>
<td>Every 21 days for up to 3 cycles</td>
<td></td>
</tr>
<tr>
<td>2,9</td>
<td>Folinic acid</td>
<td>15mg</td>
<td>PO or IV</td>
<td>Every 6 hrs (total 4 doses) to start 24 hr after methotrexate on day 1 and day 8</td>
<td>Every 21 days for up to 3 cycles</td>
</tr>
</tbody>
</table>

*CISplatin is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer Here.*

*Pre and post hydration therapy required for CISplatin*

See local hospital policy recommendations.

**Suggested prehydration** for CISplatin therapy:

1. Administer 10 mmol magnesium sulphate (MgSO₄) (+/- KCl 20 mmol/L if indicated) in 1000 ml sodium chloride 0.9% over 60 minutes.
2. Administer CISplatin as described above
3. **Post hydration:** Administer 1000 ml 0.9% NaCl over 60 mins
4. 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 0-1

**EXCLUSIONS:**

- Hypersensitivity to methotrexate, vinBLAStine, CISplatin or any of the excipients
- Moderate/severe renal impairment (creatinine clearance < 60 mL/min)
- Pregnancy and Lactation
- Pre existing neuropathies ≥ grade 2
- 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
- Audiology and creatinine clearance if clinically indicated

Regular tests:
- FBC, renal and liver profile prior to each cycle
- FBC and renal profile Day 8

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

<table>
<thead>
<tr>
<th>ANC (x10⁹ /L)</th>
<th>Platelets (x10⁹ /L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.5</td>
<td>and ≥100</td>
<td>100% Dose</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>or &lt;100</td>
<td>Hold* until recovery</td>
</tr>
<tr>
<td>Febrile neutropenia or ANC &lt; 0.5</td>
<td>or &lt; 50</td>
<td>Hold* until recovery then 75% of previous dose</td>
</tr>
</tbody>
</table>

*Do not start a new cycles until ANC ≥1.5 x 10⁹/L and platelets ≥100 x10⁹/L

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician. and is subject to HSE’s terms of use available at http://www.hse.ie/eng/Disclaimer

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

### Table 2: Dose modifications in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Cr Cl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;80</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>&lt;30</td>
<td>Contra-indicated</td>
</tr>
<tr>
<td>vinBLAStine</td>
<td>No dose reduction necessary</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26-51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;51</td>
</tr>
<tr>
<td>CISplatin</td>
<td>CrCl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>≥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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CARBOplatin</td>
</tr>
</tbody>
</table>

Management of adverse events:

### Table 3: Dose Modification of CMV Therapy for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotoxicity</td>
<td>Reduce dose of CISplatin and vinBLAStine by 25% dose.</td>
</tr>
<tr>
<td>Grade 2 present at start of next cycle</td>
<td>Discontinue CISplatin and vinBLAStine</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

**EMETOGENIC POTENTIAL:**
- CISplatin: High
- Methotrexate: Low
- vinBLAStine: Minimal *(Refer to local policy).*

**PREMEDICATIONS:** None usually required

**OTHER SUPPORTIVE CARE:**
- Hydration prior and post CISplatin administration *(Reference local policy or see recommendations above).* Patient should be encouraged to drink large quantities of liquids for 24 hours after the CISplatin infusion to ensure adequate urine secretion.
- Prophylactic laxatives may be required to prevent constipation related to the use of vinca alkaloids.
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.
- **Pleural effusion or ascites:** Methotrexate should be used with caution in patients with pleural effusions or ascites, as methotrexate may accumulate in third space fluid compartments.
- **Extravasation:** vinBLASTine is a vesicant. DOXOrubicin may cause pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
- **Hypersensitivity:** Hypersensitivity reactions have been reported with CISplatin.
- **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 therapy. They should be assessed by history prior to each cycle.

DRUG INTERACTIONS:

- NSAIDs may decrease the clearance of methotrexate by decreasing its renal perfusion and tubular secretion thus increasing its toxicity.
- Sulphonamides and penicillins may displace bound methotrexate from plasma protein increasing serum methotrexate levels and its toxicity.
- Concomitant administration of drugs that cause folate deficiency may lead to increased methotrexate toxicity.
- Ciprofloxacin may inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels and its toxicity.
- Probenecid may inhibit renal excretion of methotrexate, increasing serum methotrexate levels and its toxicity.
- Co-administration of CISplatin has been reported to cause higher plasma concentrations of vinBLASTine.
- Erythromycin may increase the toxicity of vinBLASTine.
- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

- Methotrexate - L01BA01
- vinBLASTine - L01CA01
- CISplatin - L01XA01

REFERENCES:


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20/06/2016</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>20/06/2018</td>
<td>Updated with new NCCP regimen format, standardisation of treatment table updated with revised CISplatin hydration regimen recommendations</td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

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/