NCCP Chemotherapy Regimen

Gemcitabine (1000mg/m²) and CARBOplatin (AUC 5)
Therapy- 21 day

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>Treatment of patients with locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium where CISplatin is contraindicated ¹</td>
<td>C67</td>
<td>00310a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Treatment of patients with locally advanced, recurrent or metastatic non small cell lung cancer (NSCLC)²</td>
<td>C34</td>
<td>00310b</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.

Gemcitabine is administered on day 1 and day 8 and CARBOplatin on day 1 of a 21 day cycle for 4-6 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>Admin. Order</th>
<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</td>
<td>1</td>
<td>Gemcitabine</td>
<td>1000mg/m²</td>
<td>IV infusion</td>
<td>250ml NaCl 0.9% over 30mins</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>CARBOplatin</td>
<td>AUC5</td>
<td>IV infusion</td>
<td>500ml glucose 5% over 60 min</td>
<td>Every 21 days</td>
</tr>
</tbody>
</table>

CARBOplatin dose:
The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- Measured GFR (e.g. nuclear renogram) is preferred whenever feasible

Estimation of GFR (eGFR) can be done by using the Wright formula or using the Cockroft and Gault formula to measure creatinine clearance

- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight for Cockroft and Gault may be considered (4).
WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. SCr measured using enzymatic assay.

\[
GFR \text{ (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}
\]

2. SCr measured using Jaffe assay

\[
GFR \text{ (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr (micromol/min)}}
\]

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

\[
GFR \text{ (ml/min)} = S \times \frac{(140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}
\]

S= 1.04 for females and 1.23 for males

ELIGIBILITY:
- Indications as above
- ECOG 0-2
- Adequate marrow reserve (ANC > 1.5 \times 10^9/L, platelets > 100 \times 10^9/L)

EXCLUSIONS:
- Hypersensitivity to gemcitabine, CARBOplatin* or any of the excipients
- Pregnancy or Breast Feeding
  *If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/HDU supervision (5).

PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Medical Oncologist
NCCP Chemotherapy Regimen

TESTS:

**Baseline tests:**
- FBC, renal and liver profile
- Audiometry and creatinine clearance as clinically indicated

**Regular tests:**
- Day 1: FBC, renal and liver profile
- Day 8: FBC, renal profile

**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:
Prior to commencing a new treatment cycle (i.e day 1), ANC must be >1x10^9/L and platelets >100x10^9/L

Dose modifications for gemcitabine within a cycle (i.e day 8)

<table>
<thead>
<tr>
<th>ANC (x 10^9 /L)</th>
<th>Platelet count (x 10^9 /L)</th>
<th>Other toxicity</th>
<th>Recommended dose of Gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1</td>
<td>and</td>
<td>&gt;100</td>
<td>100%</td>
</tr>
<tr>
<td>0.5-1</td>
<td>or</td>
<td>50-100</td>
<td>75%</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>or</td>
<td>&lt;50</td>
<td>Omit. Do not restart treatment until ANC &gt; 0.5 and platelets &gt; 50</td>
</tr>
<tr>
<td>ANC &lt; 0.5 for &gt;5 days or ANC &lt; 0.1 for &gt; 3 days or Any incidence of febrile neutropenia</td>
<td>or</td>
<td>&lt;25</td>
<td>cycle delay of &gt;1 week due to any toxicity</td>
</tr>
</tbody>
</table>
Renal and Hepatic Impairment:

Table 2: Dose modification of CARBOplatin and Gemcitabine in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
</table>
| CARBOplatin   | • Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.  
               | • In case of GFR ≤ 20ml/min carboplatin should not be administered at all.        | Probably no dose modification required |
|               | • If Cockroft & Gault or Wright formula are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration. |
|               | • If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockroft & Gault or Wright formulae taking care this does result in a dose reduction. |
| Gemcitabine   | CrCl (ml/min) Dose                                                                 | Hepatic Impairment                  |
|               | >30 100%                                                                         | AST elevations do not seem to cause dose limiting toxicities. If bilirubin > 27 μmol/L, initiate treatment with dose of 800 mg/m². |
|               | <30 Consider dose reduction clinical decision                                      |                                     |

Management of adverse events:

Table 3: Dose Modification schedule for Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 Non-haematological toxicity (except nausea/vomiting)</td>
<td>Therapy with gemcitabine and CARBOplatin should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with dose reduction at discretion of prescribing consultant.</td>
</tr>
<tr>
<td>Grade ≥ 2 pneumonitis</td>
<td>Discontinue gemcitabine</td>
</tr>
</tbody>
</table>

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Gemcitabine Low (Refer to local policy).

CARBOplatin High (Refer to local policy).

PREMEDICATIONS: None usually required

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**: Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
- **Pulmonary Toxicity**: Acute shortness of breath may occur with gemcitabine. Discontinue treatment with gemcitabine if drug-induced pneumonitis is suspected.
- **Cardiovascular**: Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events
- **Hypersensitivity**: Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity**: Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as paraesthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

DRUG INTERACTIONS:

- CARBOplatin 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:

- Gemcitabine: L01BC05
- CARBOplatin: L01XA02

REFERENCES:

5. NCCN Guidelines Version3.2017 Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
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

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NCCP Regimen: Gemcitabine and CARBOplatin (AUC 5)-21 day
Tumour Group: Genitourinary/Lung
NCCP Regimen Code: 00310

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Review: 06/11/2021

Version number: 3

Version | Date | Amendment | Approved By
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1 | | | Prof Maccon Keane
2 | 15/11/2017 | Updated title and dosing in renal and hepatic impairment. Emetogenic status of CARBOplatin amended from moderate to moderate to high Applied new NCCP regimen template | Prof Maccon Keane
3 | 06/11/2019 | Reviewed. Treatment table standardised, updated emetogenic potential and management of adverse events | Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

1 This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital’s policy on the use of unlicensed medication and unlicensed or “off label” indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or “off label” indication has been acknowledged by the hospital’s Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.