Chemotherapy Protocol

BLADDER

CISPLATIN (70)-GEMCITABINE

Regimen

Bladder-Cisplatin (70)-Gemcitabine

Indication

First line treatment of locally advanced or metastatic urothelial cancer

Adjuvant / Neo-adjuvant treatment of urothelial cancer

WHO performance status 0, 1, 2

Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Neuropathy, nephrotoxicity, ototoxicity</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Peripheral oedema, diarrhoea, constipation, rash, respiratory problems, influenza like symptoms, radiosensitising</td>
</tr>
</tbody>
</table>

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day 1 and 8 of treatment
- Calculated or measured creatinine clearance prior to each cycle. EDTA may be considered prior to cycle 1 or if there are significant changes in renal function during treatment.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.
### Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

**Day 1**

<table>
<thead>
<tr>
<th>Neutrophils (x10^9/L)</th>
<th>Dose Modifications (cisplatin and gemcitabine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or greater</td>
<td>100%</td>
</tr>
<tr>
<td>less than 1</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Occurrence. Delay until recovery</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Occurrence Delay until recovery then give 75% of the original dose</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Occurrence Delay until recovery and then re-start treatment using 75% of the original dose</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>Dose Modifications (cisplatin and gemcitabine)</td>
</tr>
<tr>
<td>100 or greater</td>
<td>100%</td>
</tr>
<tr>
<td>Less than 100</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Occurrence. Delay until recovery then give 75% of the original dose</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Occurrence Delay until recovery then give 50% of the original dose</td>
</tr>
</tbody>
</table>

**Day 8**

<table>
<thead>
<tr>
<th>Neutrophils (x10^9/L)</th>
<th>Dose Modifications (gemcitabine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or greater</td>
<td>100%</td>
</tr>
<tr>
<td>0.5 - 1</td>
<td>75%</td>
</tr>
<tr>
<td>less than 0.5</td>
<td>Omit</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>Dose Modifications (gemcitabine)</td>
</tr>
<tr>
<td>100 or greater</td>
<td>100%</td>
</tr>
<tr>
<td>50 - 100</td>
<td>75%</td>
</tr>
<tr>
<td>less than 50</td>
<td>Omit</td>
</tr>
</tbody>
</table>

If dose modifications to gemcitabine dose are required on day 1 then continue with the reduced dose for day 8.
Bladder - Cisplatin (70) - Gemcitabine

Hepatic Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin μmol/L</th>
<th>AST/ALT units/L</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>N/A</td>
<td>N/A</td>
<td>No dose adjustment needed</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>30 or greater*</td>
<td>N/A</td>
<td>Initiate treatment with a dose of 800mg/m²</td>
</tr>
</tbody>
</table>

*Limit reflects local practice and may vary from published sources

Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>60 or greater</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>40-59</td>
<td>Consider cisplatin (35)-gemcitabine (split dose cisplatin)</td>
</tr>
<tr>
<td></td>
<td>39 or below</td>
<td>Consider alternative</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>30 or greater</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>less than 30</td>
<td>Consider dose reduction</td>
</tr>
</tbody>
</table>

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 75% of the original dose or discontinued as appropriate.

Regimen

21 day cycle for 3 - 6 cycles (3 cycles will be set in Aria)

First line treatment - 6 cycles

Adjuvant - 4 cycles

Neoadjuvant - 3 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>70mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a rate of cisplatin of 1mg/min (minimum 120 minutes)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000mg/m²</td>
<td>1 and 8</td>
<td>Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes</td>
</tr>
</tbody>
</table>
Dose Information

- Cisplatin will be dose banded according to the CSCCN agreed bands
- Gemcitabine will be dose banded according to the CSCCN agreed bands

Administration Information

Extravasation

- Cisplatin – exfoliant
- Gemcitabine – neutral

Additional Therapy

- Antiemetics
  
  15-30 minutes prior to chemotherapy on **day 1**
  - aprepitant 125mg oral
  - dexamethasone 4mg oral or intravenous
  - ondansetron 8mg oral or intravenous

  As take home medication on **day 1**
  - aprepitant 80mg oral daily for on days 2 and 3
  - dexamethasone 4mg oral once a day for 3 days
  - metoclopramide 10mg oral three times a day as required (supply for day 1 and 8)
  - ondansetron 8mg oral twice a day for 3 days

  15-30 minutes prior to chemotherapy on **day 8**
  - metoclopramide 10mg oral or intravenous

- Cisplatin pre and post hydration as follows

  Pre

  Furosemide 40mg oral or intravenous

  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Post

  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

  Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.
- Mouthwashes according to local or national policy on the treatment of mucositis
- Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Coding (OPCS 4.6)

- Procurement – X70.5
- Delivery – X72.1 & X72.4

References
REGIMEN SUMMARY

Cisplatin (70)-Gemcitabine

Cycle One and Two

Day 1

1. Aprepitant 125mg oral
2. Dexamethasone 4mg oral or intravenous
3. Ondansetron 8mg oral or intravenous
4. Furosemide 40mg oral or intravenous
5. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes
6. Gemcitabine 1000mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
7. Cisplatin 70mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion at a rate of cisplatin of 1mg/min (minimum 120 minutes)
8. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol with potassium chloride 20mmol intravenous infusion over 60 minutes

Take Home Medicines

9. Aprepitant 80mg once a day on days 2 and 3 oral
10. Dexamethasone 4mg once a day for 3 days oral starting on day two of the chemotherapy
11. Metoclopramide 10mg three times a day when required for nausea oral

Administration Instructions
Please supply 10 days or an original pack if appropriate to cover Day 1 and Day 8.

12. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

Day 8

13. Metoclopramide 10mg oral or intravenous
14. Gemcitabine 1000mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
Cycle Three

Day 1

15. Warning – check number of cycles

16. Aprepitant 125mg oral

17. Dexamethasone 4mg oral or intravenous

18. Ondansetron 8mg oral or intravenous

19. Furosemide 40mg oral or intravenous

20. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol and potassium chloride 20mmol intravenous infusion over 60 minutes

21. Gemcitabine 1000mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes.

22. Cisplatin 70mg/m² in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion at a rate of cisplatin of 1mg/min (minimum 120 minutes)

23. Sodium chloride 0.9% 1000ml with magnesium sulphate 16mmol with potassium chloride 20mmol intravenous infusion over 60 minutes

Take Home Medicines

24. Aprepitant 80mg once a day on days 2 and 3 oral

25. Dexamethasone 4mg once a day for 3 days oral starting on day two of the chemotherapy

26. Metoclopramide 10mg three times a day when required for nausea oral

Administration Instructions
Please supply 10 days or an original pack if appropriate to cover Day 1 and Day 8.

27. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

Day 8

28. Metoclopramide 10mg oral or intravenous

29. Gemcitabine 1000mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts:

- Hampshire Hospitals NHS Foundation Trust
- NHS Isle of Wight
- Portsmouth Hospitals NHS Trust
- Salisbury Hospitals NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.