

Chemotherapy Protocol
BILIARY TRACT CANCER
CISPLATIN-GEMCITABINE

Regimen

- Biliary Tract Cancer – Cisplatin-Gemcitabine

Indication

- First line therapy of locally advanced / metastatic biliary tract cancer
- WHO performance status 0, 1, 2
- Palliative intent

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Gemcitabine	Diarrhoea, constipation, rash, respiratory problems (pneumonitis), influenza like symptoms, radiosensitising, transient elevation of LFTs

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

Monitoring

Regimen

- FBC, LFT's and U&E's prior to day 1 and 8 of each cycle (consider measured GFR prior to cycle one if the calculated renal function is less than 45ml/min).

Dose Modifications

The dose modifications listed are for haematological, liver and renal function 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. The following is a general guide only.

Haematological

Prior to prescribing on day one of cycle one the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1 \times 10^9/L$
Platelets	equal to or more than $100 \times 10^9/L$

Consider blood transfusion if patient symptomatic of anaemia or haemoglobin of less than 10g/dL

In order to proceed with administration of the full dose of gemcitabine on days 1 and 8 of each cycle the neutrophil count must be greater than or equal to $1 \times 10^9/L$ and the platelets greater than or equal to $100 \times 10^9/L$. On the day of treatment if the neutrophil count is $0.5 - 0.9 \times 10^9/L$ and / or the platelet $50 - 99 \times 10^9/L$ the gemcitabine should be given at 75% of the original dose, cisplatin should be given at the full dose. If the neutrophil count is less than or equal to $0.49 \times 10^9/L$ and / or the platelet count is less than or equal to $49 \times 10^9/L$ defer both agents for 7 days and review.

Hepatic Impairment

Drug	Bilirubin $\mu\text{mol/L}$	AST/ALT units	Dose (% of original dose)
Cisplatin	No adjustment necessary		
Gemcitabine	AST elevations do not seem to cause dose limiting toxicities. If bilirubin is greater than $27 \mu\text{mol/L}$, initiate treatment with dose of 800 mg/m^2 .		

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin	more than 60	100
	45-59	75
	less than 45	Consider carboplatin
Gemcitabine	Consider dose adjustments if the CrCl is less than 30ml/min	

Other

If due to toxicity treatment is to be deferred, this should be for 7 days in the first instance (note this does not apply to biliary tract obstruction). If a decision is made to defer the gemcitabine, the cisplatin will also be deferred (i.e. cisplatin will not be administered as a single agent). If a second deferral is required, the treatment week in question is omitted and the patient will move on to the next treatment point (not necessarily next cycle).

No dose modifications are required for alopecia or CTC grade 1 – 2 lethargy, nausea, vomiting or oedema. Rather symptomatic therapy should be tried in the first instance.

If lethargy occurs at CTC grade 3 – 4 administer gemcitabine at 75% of the original dose. If the lethargy continues at this level despite the dose reduction then stop treatment.

For grade CTC 3 – 4 nausea and / or vomiting that does not respond to optimisation of anti-emetic therapy delay treatment until recovery and then omit the cisplatin. If this is insufficient to control the symptoms administer the gemcitabine at 75% of the original dose.

Oedema is a complication of gemcitabine. If this occurs at CTC grade 3 – 4 delay all treatment until recovery to baseline then re-start treatment using gemcitabine at 75% of the original dose. If the oedema fails to respond to this dose modification then stop treatment.

For CTC grade 1 – 2 peripheral neuropathy delay the cisplatin until recovery to baseline then continue treatment at the original dose. There is no need to modify the dose of gemcitabine. For CTC grade 3 – 4 neuropathy or CTC grade 1 -2 that does not recover stop the cisplatin therapy and continue with single agent gemcitabine.

There is no need to modify doses for tinnitus that resolves between cycles. If the tinnitus persists omit the cisplatin and continue with single agent gemcitabine.

In the event of the development of obstructive jaundice due to biliary tract obstruction, appropriate measures will be undertaken to diagnose and relieve the obstruction. Defer chemotherapy until the liver function tests have improved to the pre-treatment eligibility levels (i.e. total bilirubin less than or equal to 1.5xULN; ALT, AST & alkaline phosphatase less than or equal to 5xULN). Chemotherapy may then resume at the start of the next treatment cycle.

[Regimen](#)

21 day cycle for 4 cycles

Drug	Dose	Days	Administration
Cisplatin	25mg/m ²	1, 8	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/min (minimum time 60 minutes)
Gemcitabine	1000mg/m ²	1, 8	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Dose Information

- Cisplatin will be dose banded as per the CSCCN agreed bands.
- Gemcitabine will be dose banded as per the CSCCN agreed bands.

Administration Information

Extravasation

- Cisplatin - exfoliant
- Gemcitabine – neutral

Additional Therapy

- Antiemetics

15-30 minutes prior to chemotherapy

- dexamethasone 8mg oral or intravenous
- ondansetron 8mg oral or intravenous

As take home medication;

- dexamethasone 4mg twice a day oral for 3 days
- metoclopramide 10mg three times a day when required (day 1 only)
- ondansetron 8mg twice a day oral for 3 days

- 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.

- 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

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

References

1. Valle J, Wasan H, Palmer DH et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010; 362 (14): 1273-1281.

REGIMEN SUMMARY

Cisplatin-Gemcitabine

Day One

1. Dexamethasone 8mg oral or intravenous
2. Ondansetron 8mg oral or intravenous
3. Furosemide 40mg when required oral or intravenous
4. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes
5. Gemcitabine 1000mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
6. Cisplatin 25mg/m² intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 60 minutes)
7. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Take Home Medicines (day one only)

8. Dexamethasone 4mg twice a day oral for 3 days starting on the day following chemotherapy
9. Metoclopramide 10mg three times a day when required oral
10. Ondansetron 8mg twice a day oral for 3 days starting on the evening of the day of chemotherapy

Day Eight

11. Dexamethasone 8mg oral or intravenous
12. Ondansetron 8mg oral or intravenous
13. Furosemide 40mg when required oral or intravenous
14. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes
15. Gemcitabine 1000mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
16. Cisplatin 25mg/m² intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 60 minutes)

17. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Take Home Medicines (day eight only)

18. Dexamethasone 4mg twice a day oral for 3 days starting on the day following chemotherapy

19. Ondansetron 8mg twice a day oral for 3 days starting on the evening of the day of chemotherapy

The metoclopramide is not listed as a day eight TTO as the patient is likely to have supplies left from day one. They should be counselled to use the metoclopramide as per day one of the cycle.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Feb 2014	Header changed to NHS badge In name "and" replaced with dash Adverse effects put in table and toxicity removed < and > written in full Dose modification tabulated Renal and hepatic function tabulated and updated Regimen tabulated Twice daily changed to twice a day etc Regimen name added to summary Summary re-numbered Metoclopramide dose changed to 10mg Stat removed Bolus removed Timing of TTO antiemetics added to the summary Document control tabulated Hospital representation and disclaimer added	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Dec 2010	Day 8 antiemetics added to the summary section	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician

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 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.