GEMCITABINE AND CISPLATIN

For advanced or metastatic biliary tract tumours, including gallbladder carcinoma and cholangiocarcinomas

Drug/Dose:	Cisplatin	25mg/m^2	IV	Day 1 and Day 8
	Gemcitabine	1000mg/m^2	IV	Day 1 and Day 8

Administration:
1 litre 0.9% Sodium Chloride + 20mmol KCl + 10mmol $MgSO_4$ IV over 2 hours
Mannitol 20% 100ml IV over 15 minutes
Cisplatin in 500ml 0.9% Sodium Chloride IV over 1 hour
500mls water orally over 1 hour
concurrently with:
Gemcitabine diluted in 250 ml 0.9% Sodium Chloride over 30 minutes

Frequency:
Repeat every 21 days
Review prior to each cycle, and prior to Day 8 chemotherapy if there is a problem
Treat, for a maximum of 8 cycles, until no further clinical benefit, excessive toxicity or evidence of progression

Main Toxicities:
myelosuppression; neuropathy; ototoxicity; nephrotoxicity;
erythematous rash; peripheral oedema (mild-moderate & reversible);
flu-like syndrome; ovarian failure/infertility

Anti-emetics:
highly emetogenic

Extravasation:
non vesicants

Regular Investigations:	FBC	Day 1 & Day 8
	U&Es	Day 1 & Day 8
	Mg^{2+} and Ca^{2+}	Day 1 & Day 8
	LFTs	Day 1
	EDTA	Prior to 1st cycle
	CA 19-9	Day 1

Comments:
For patients on Cycle 1 whose EDTA is not yet available, Cockcroft & Gault may be used to predict GFR. Cisplatin dose should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml Sodium Chloride 0.9% IV +/- furosemide 20 – 40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload. The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Reason for Update: reference updated; carbo substitution info added	Approved by Lead Chemotherapy Nurse: P Deery
Version: 4	Approved by Consultant: Dr S Cummins
Supersedes: Version 3	Date: 24.6.13
Prepared by: S Taylor	Checked by: C Tucker

Check electrolytes – additional supplementation of magnesium, calcium or potassium may be required.

Dose Modifications

Haematological Toxicity:

Day 1* and Day 8:

Neutrophils		Platelets	Gemcitabine Dose	Cisplatin Dose (for carbo, see below)
> 1.0 x 10^9/l	**and**	> 100 x 10^9/l	Give 100% dose	Give 100% dose
0.5 – 1.0 x 10^9/l	**or**	50 – 100 x 10^9/l	Give 75% dose	Give 100% dose
< 0.5 x 10^9/l	**or**	< 50 x 10^9/l	Defer 1 week	Defer 1 week

If a dose reduction to 75% has been made for gemcitabine, then the dose should be increased to 100% on the subsequent doses, providing the FBC returns to within normal limits.

* If substituting with carboplatin, Day 1 treatment should only be given if neutrophils ≥ 1.5 x 10^9/l and platelets ≥ 100 x 10^9/l.

Non-Haematological Toxicity: For any Grade 3 – 4 toxicity, treatment should be deferred until recovery, and then continued with an appropriate dose reduction.

Renal Impairment: NB. Cisplatin is both eliminated primarily (> 90%) in the urine and is itself nephrotoxic.

CrCl (ml/min)	Cisplatin Dose
≥ 60	Give 100%
45 – 59	Give 75%
20 - 44	Cisplatin contra-indicated Carboplatin AUC 5 on **Day 1 only**, administered in 250ml 5% Glucose over 30 minutes, may be substituted. It may be given according to this protocol, with however no requirement for pre- or post-hydration, nor fluid balance/urine monitoring
< 20	Carboplatin contra-indicated

If CrCl < 30ml/min, consider gemcitabine dose reduction – clinical decision

Hepatic Impairment: If bilirubin > 27 µmol/L, initiate treatment with gemcitabine 800mg/m^2
BUT
If bilirubin > 30µmol/l or ALT / ALP > 3 x ULN (> 5 x ULN if liver metastases are present), treatment should be deferred unless approved by Consultant. These patients are at high risk of potentially fatal sepsis.

Neurotoxicity: Seek further advice if the patient reports symptoms indicative of neurotoxicity (paraesthesias, difficulty with motor control) or ototoxicity (tinnitus, deafness).

References: Valle, J et al; NEJM 2010; 362: 1273 – 1281