Systemic Anti Cancer Therapy Protocol

GemPOx
Intracranial Germ Cell

PROTOCOL REF: MPHAGPOGC
(Version No: 1.0)

Approved for use in:

CNS germ cell tumours

Refractory to initial chemotherapy

PS 0 – 1

Dosage:

Drug	Dose	Route	Frequency
Gemcitabine	**800mg/m^2**	IV infusion	Day 1 of a 14 day cycle
Paclitaxel	**170mg/m^2**	IV infusion	Day 1 of a 14 day cycle
Oxaliplatin	**100mg/m^2**	IV infusion	Day 1 of a 14 day cycle

Treatment is repeated every 14 days for 2 cycles, if sufficient response then continue to 4 cycles

Stem cell harvesting can be considered after cycle 1 or cycle 2

Emetogenic risk (if applicable):

Mild/moderate or severely emetogenic.

Supportive treatments:

Ondansetron 8mg orally twice a day for three days

Dexamethasone 4mg orally twice a day for three days

Domperidone 10mg tablets, three times a day as required

Filgrastim subcutaneous injection daily for 7 days from day 3 (dose of 300 micrograms for patients below 70kg, and 480 micrograms for those 70kg and above)

Extravasation risk (if applicable):

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Gemcitabine – neutral

Oxaliplatin – irritant

Paclitaxel - vesicant

Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="3">Renal</td><td>Paclitaxel</td><td colspan="2">No adjustment necessary</td></tr>
<tr><td>Oxaliplatin</td><td colspan="2"><table><tr><th>Creatinine Clearance (mL/min)</th><th>Oxaliplatin Dose</th></tr><tr><td>>50</td><td>Give 100%</td></tr><tr><td>30 to 50</td><td>Max 85mg/m^2</td></tr><tr><td><30</td><td>Omit</td></tr></table></td></tr>
<tr><td>Gemcitabine</td><td colspan="2">No safety data in patients with CrCl < 30ml/min. Consider dose reduction (clinical decision).</td></tr>
<tr><td rowspan="3">Hepatic</td><td>Paclitaxel</td><td colspan="2"><table><tr><td>Bilirubin less than 1.25 times ULN and AST < 10 x ULN</td><td>Give 100% dose</td></tr><tr><td>Bilirubin greater than 1.25 times ULN</td><td>Consider dose reduction</td></tr><tr><td>Alk Phos more than 3 times ULN</td><td>Consider dose reduction</td></tr></table></td></tr>
<tr><td>Oxaliplatin</td><td colspan="2">If bilirubin is more than 3 times ULN will require dose reduction to 50%</td></tr>
<tr><td>Gemcitabine</td><td colspan="2">No safety data in patients with hepatic impairment. If bilirubin > 27µmol/L, consider reducing dose</td></tr>
</table>

Interactions:

Antiepileptics (CYP 3A4 inducers)

Phenytoin, carbamezapine and phenobarbital increase the clearance of paclitaxel and increase its maximum tolerated dose.

Ciclosporin

Levels of paclitaxel increased after oral administration of ciclosporin.

Fluconazole/Ketoconazole (CYP3A4 inhibitors)

Paclitaxel levels may be increased

Quinine and verapamil

Paclitaxel levels possibly increased.

Warfarin/coumarin anti-coagulants – can increase anticoagulant effect or cause fluctuations. Avoid if possible or consider switching patient to a LMWH during treatment. If patient continues to take an oral anticoagulant, INR must be checked at least once a week and dose adjusted accordingly.

Gemcitabine is a radio-sensitiser.

QT prolongation

Caution with oxaliplatin in patients on concurrent medications known to prolong QT interval.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Chlorphenamine**	**10mg**	**IV**	30 mins before chemotherapy
	Dexamethasone	**16.5mg**	**IV**	30 mins before chemotherapy
	Ranitidine	**50mg**	**IV**	30 mins before chemotherapy
	Ondansetron	**16mg**	**PO**	30 mins before chemotherapy
	Paclitaxel	**170mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 3 hours
	Gemcitabine	**800mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 60 minutes
	Oxaliplatin	**100mg/m^2**	**IV**	Glucose 5% 500mL over 2 hours

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, peripheral neuropathy, allergic infusion reactions, rash.

Comments: Premedication treatment of chlophenamine, dexamethasone and ranitidine is given prior to paclitaxel to reduce the risk of hypersensitivity. Paclitaxel reactions commonly occur within the first few minutes of starting the infusion most likely with the first two cycles.

Oxaliplatin	
Acute cold related dysesthesia (CRD)	Transient paraesthesia of hands and feet as well as laryngopharyngeal dysesthesia (unpleasant sensations in throat) is common. Onset is during or within hours of infusion and it resolves in minutes or days. Symptoms are exacerbated by cold – advise patients on suitable precautions e.g. avoid cold drinks. Should not require dose reduction, but if troublesome then infusion duration can be increased to 6 hours (see note below).
Laryngopharyngeal dysaesthesia	Stop infusion, provide symptomatic treatment. Resume at slower infusion rate. Give subsequent infusions over 6 hours (see note below).

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Prior to cycle 3	Cycle 3	Cycle 4	Ongoing
Informed Consent	X						
Clinical Assessment	X		X		X		Every cycle
SACT Assessment (to include PS and toxicities)	X	X	X		X	X	Every cycle
FBC	X	X	X		X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X		X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X		X	X	Every cycle
MRI scan	X			X			At the end of treatment
AFP, beta HCG, LDH	X		X		X	X	If clinically indicated
Blood pressure measurement	X	X	X		X	X	Repeat if clinically indicated
Weight recorded	X	X	X		X	X	Every cycle
Height recorded	X						
Blood glucose	X						Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity (if required):

Proceed on day 1 if-

ANC ≥ 0.75 x 10^9/L	Plt ≥ 75 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.74 x 10^9/L	Plt ≤ 74 x 10^9/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity (if required):

For grade 2 peripheral neuropathy consider 20% dose reduction of paclitaxel and oxaliplatin.

References:

1. https://www.medicines.org.uk/emc
2. Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)
3. Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)
4. Clinical trial protocol NIH www.cancer.gov, NCT01270724 Gemcitabine, paclitaxel, oxaliplatin, high dose chemotherapy and stem cell transplant in treating patients with recurrent or refractory CNS germ cell tumours
5. Perez-Somarriba Pediatr Blood Cancer 2020: 67, 28089
6. Bokemeyer C, Annals of Oncology 2008 19:448-453