PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

DDGP
Dexamethasone, Cisplatin, Gemcitabine and Peg-aspargase
NK T Cell Lymphoma

PROTOCOL REF: MPHADDGP
(Version No. 1.0)

Approved for use in:

Extranodal Natural Killer (NK) T Cell Lymphoma.

Blueteq registration is NOT required

Dosage:

Drug	Dose	Route	Frequency
Dexamethasone	**15 mg/m^2**	IV infusion	Day 1 to 5 (NB day 5 could be given orally to prevent admission to the day ward)
Cisplatin	**20 mg/m^2**	IV infusion	Days 1 to 4
Gemcitabine	**800mg/m^2**	IV infusion	Days 1 and 8
Peg-aspargase	**2500 units/m^2**	IV infusion	Day 1 only

Cycle length every 21 days. Maximum 6 cycles.

Administration:

- Possible life threatening anaphylaxis and anaphylactoid reactions can occur with peg-aspargase. The patient should be monitored for an hour after administration.
- Peg-aspargase (Oncaspar®) may cause central nervous system signs and symptoms manifesting as somnolence, confusion, convulsions. Patients should be monitored closely.

- Peg-aspargase can cause fluctuations in coagulation factors – monitor closely for signs of bleeding/clots.
- Furosemide 20-40mg may be added if weight gain >2kgs during infusion on day 1 to 4.
- Ensure urine output is >100ml/hr before starting cisplatin. Patients should drink 3L of fluid in the 24 hours after their cisplatin infusion.
- IV hydration is required pre and post cisplatin administration.
- Patient should report any changes in hearing or balance.

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

Pre-infusion medicines:

- Ondansetron IV 8mg on day 1

Supportive medicines:

- Allopurinol PO 100mg or 300mg daily (depending on renal function) for first cycle
- Aprepitant 125mg D1, 80mg D2 and D3
- Co-trimoxazole PO 480mg once daily
- Filgrastim S/C 30 or 48 million units once daily for 5 days starting on day 9 (30million units if <70kgs and 48 million units >70kgs)
- Metoclopramide PO 10mg three times daily prn
- Ondansetron PO 8mg twice daily on days 1 to 5 and 8 to 10

Extravasation risk:

- Gemcitabine: non-vesicant
- Cisplatin: irritant
- Pegaspargase: neutral

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

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
Gemcitabine	No dose adjustment required but for haemodialysis patients start dialysis 6 to 12 hours after gemcitabine	
Cisplatin	**CrCl (ml/min)**	**Dose**
	50-59	75%
	40-49	50%
	<40	Not recommended; consider carboplatin
	Haemodialysis	Consider 50%
Pegaspargase	No dose adjustment needed	

Hepatic Dose Modifications	
Gemcitabine	If bilirubin is >27 micromol/L then consider starting at 80% dose and increase as tolerated. Alternatively start at usual dose and monitor closely.
Cisplatin	No dose adjustment needed
Pegaspargase	No dose adjustment needed

Interactions:

Gemcitabine

- Gemcitabine is a radiosensitiser therefore extreme care is required is a patient is receiving concurrent radiotherapy.

Cisplatin

- Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, Amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on the kidneys and auditory function.

- Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control when phenytoin is given as current treatment. During cisplatin therapy starting new anticonvulsant treatment with phenytoin is strictly contraindicated.

Pegaspargase

- The decrease in serum proteins caused by pegaspargase can increase the toxicity of other medicinal products that are protein bound e.g. amiodarone, atovaquone, amitriptyline and warfarin
- In addition, by inhibiting protein synthesis and cell division, pegaspargase can disturb the mechanism of action of other substances which require cell division for their effect, e.g., methotrexate.
- Pegaspargase can interfere with metabolism and clearance of other medicinal products, based on its effects on protein synthesis and hepatic function, as well as from its combined use with other chemotherapy products known to interact with CYP enzymes.
- The use of pegasparage can lead to fluctuation in coagulation factors. This can promote the tendency to bleeding and/or thrombosis. Caution is therefore needed when anticoagulants such as warfarins, heparin, dipyridamole, aspirin or non-steroidal anti-inflammatory medicinal products are given concomitantly, or when concomitant chemotherapy regimen including methotrexate, daunorubicin, corticosteroids is administered.
- When glucocorticoids (e.g. dexamethasone) and pegaspargase are given at the same time, alterations in coagulation parameters (e.g., fall in fibrinogen and antithrombin III deficiency, ATIII) can be more pronounced.
- An indirect interaction cannot be ruled out between pegaspargase and oral contraceptives due to pegaspargase hepatotoxicity that may impair the hepatic clearance of oral contraceptives. Therefore, the concomitant use of pegaspargase with oral contraceptives is not recommended. Another method than oral contraception should be used in women of childbearing potential.

For more detailed interactions please refer to the SPC

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant**	**125mg**	**PO**	60 minutes before chemotherapy
	Ondansetron	**8mg**	**IV**	30 minutes before chemotherapy
	Dexamethasone	**15mg/m^2**	**IV**	Over 5 minutes
	Peg-aspargase	**2500 unit/m^2**	**IV**	In 100mLs sodium chloride 0.9% over 2 hours alongside a fast flowing infusion of sodium chloride 0.9%. Monitor for infusion related reactions during infusion and for one hour post infusion
	Gemcitabine	**800 mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
	Pre-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour
	Cisplatin	**20mg/m^2**	**IV**	In 1000mLs sodium chloride 0.9% over 2 hours. Cisplatin must be started after the gemcitabine. Ensure urine output >100mL/hr before starting cisplatin
	Post-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour
2	**Aprepitant**	**80mg**	**PO**	60 minutes before chemotherapy
	Dexamethasone	**15mg/m^2**	**IV**	Over 5 minutes
	Pre-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour
	Cisplatin	**20mg/m^2**	**IV**	In 1000mLs sodium chloride 0.9% over 2 hours. Cisplatin must be started after the gemcitabine. Ensure urine output >100mL/hr before starting cisplatin
	Post-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour
3	**Aprepitant**	**80mg**	**PO**	60 minutes before chemotherapy
	Dexamethasone	**15mg/m^2**	**IV**	Over 5 minutes
	Pre-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour

	Cisplatin	**20mg/m²**	**IV**	In 1000mLs sodium chloride 0.9% over 2 hours. Cisplatin must be started after the gemcitabine. Ensure urine output >100mL/hr before starting cisplatin
	Post-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour
4	**Dexamethasone**	**15mg/m²**	**IV**	Over 5 minutes
	Pre-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour
	Cisplatin	**20mg/m²**	**IV**	In 1000mLs sodium chloride 0.9% over 2 hours. Cisplatin must be started after the gemcitabine. Ensure urine output >100mL/hr before starting cisplatin
	Post-hydration			
	Sodium chloride 0.9%	**500mLs**	**IV**	Over 1 hour
5	**Dexamethasone**	**15mg/m²**	**IV or PO**	Over 5 minutes
8	**Gemcitabine**	**800 mg/m²**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes

Main toxicities:

Cisplatin
Nephrotoxicity - ensure adequate pre and post hydration is prescribed. Ototoxicity - assess patient for tinnitus or hearing abnormalities Bone marrow suppression – anaemia, thrombocytopenia, neutropenia. Nausea, vomiting, diarrhea.
Gemcitabine
Bone marrow suppression – anaemia, thrombocytopenia, neutropenia Headache, insomnia, somnolence, cough, dyspnea, nausea, vomiting, diarrhea, constipation, myalgia, rash, raised LFTs and bilirubin, haematuria, fever, fatigue
Peg-asparagase
Peg-asparagase is associated with numerous toxicities including hepatic dysfunction, coagulopathy and thrombo-haemorrhagic complications, pancreatitis, hyperglycaemia and hyperlipidaemia. Hypersensitivity including anaphylactic reactions can occur during the therapy, the patient should be monitored for an hour after administration. In case of hypersensitivity reactions, change to Erwinase ®. Somnolence, confusion, convulsions. Neurotoxicity (including reversible posterior leukoencephalopathy syndrome)

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 1 D8	Cycle 2	Cycle 2 D8	Cycle 3	Cycle 3 D8	Ongoing
Informed Consent	x							
Clinical Assessment	x			x		x		Every cycle
SACT Assessment (to include PS and toxicities)	x	x		x		x		Every cycle
FBC	x	x	x	x	x	x	x	Every cycle
U&E & LFTs	x	x		x		x		Every Cycle
CrCl (Cockcroft and Gault)	x	x		x		X		Every cycle
Amylase, clotting screen, fibrinogen, glucose, ammonia	x							Monitor regularly during treatment with peg-aspargase
CT or PET-CT scan	x							And baseline and thereafter as clinically indicated.
ECG								If clinically indicated
Blood pressure measurement	x							Repeat if clinically indicated
Respiratory Rate								If clinically indicated
Weight recorded	x	x		x		x		Every cycle
Blood glucose	x							Repeat if clinically indicated
Pregnancy test	x							If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 and 8 if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

NB treatment can continue without dose modifications if cytopenias are thought to be due to disease infiltration

Day of cycle	Parameter (x 10^9/L)	Action
1	ANC ≥ 1.0 and platelets < 75	Delay 1 week. Then if platelets ≥ 50, give 100%. Support with platelet transfusions as necessary.
	ANC < 1.0 and platelets ≥ 75	Delay 1 week. If ANC then ≥ 0.5, proceed with 100% and support with GCSF
	ANC < 1.0 and platelets < 75	Delay 1 week. If ANC then ≥ 0.5 and platelets ≥ 50, give 100% dosing. Support with GCSF and/or transfusions as necessary OR If ANC <0.5 and/or platelets <50 defer and check counts every 3 days. Resume when ANC ≥ 0.5 and platelets ≥50
8	ANC 0.5-1.0 and platelets ≥ 75	Give 100% gemcitabine and support with GCSF, or give 75% of original dose
	ANC ≥ 1.0 and platelets 50 to 75	Give 75% of original dose
	ANC < 0.5 and platelets < 50	Omit gemcitabine

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:

See ‘Dosing in Renal and Hepatic Impairment’

Pancreatic effects (peg-aspargase)

Peg-aspargase (Oncaspar®)	Serum amylase and/or lipase levels should be monitored frequently to identify early signs of pancreatic inflammation.	
	Suspected pancreatitis	Suspend peg-aspargase. If confirmed then permanently discontinue

Coagulopathy (peg-aspargase)

Serious thrombotic events, including sagittal sinus thrombosis can occur in patients receiving peg-aspargase. Discontinued in patients with serious thrombotic events.

Increased prothrombin time (PT), increased partial thromboplastin time (PTT), and hypofibrinogenaemia can occur in patients receiving peg-aspargase. Coagulation parameters should be monitored at baseline and periodically during and after treatment. When there is a marked decrease in fibrinogen or antithrombin III (ATIII) deficiency, consider appropriate replacement therapy.

Neurotoxicity / Ototoxicity (cisplatin)

Grade 2 or above should be discussed with consultant as dose reduction may be required.

References:

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3. https://www.medicines.org.uk/emc gemcitabine (accessed July 2023)
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.
5. Zhang L, Li S, Jia S, Nan F, Li Z, Cao J, Fan S, Zhang C, Su L, Wang J, Xue H, Zhang M. The DDGP (cisplatin, dexamethasone, gemcitabine, and pegaspargase) regimen for treatment of extranodal natural killer (NK)/T-cell lymphoma, nasal type.

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Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
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Version History

		Author name and designation	Summary of main changes
Aug 2023	1.0	**Aileen McCaughey – Advanced Pharmacist**	**New protocol**