SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

LYASPMEDEX
PEG ASPARAGINASE, METHOTREXATE, DEXAMETHASONE

PROTOCOL REF: MPHALYASHA
(Version No. 2.0)

Approved for use in:

- Extranodal natural killer/T-cell lymphoma

Blueteq not required

Dosage:

Drug	Dose	Route	Frequency
Methotrexate	**3000mg/m^2**	IV infusion	Day 1 (split into 300mg/m^2 over 15 minutes and then 2700mg/m^2 over 3 hours)
Dexamethasone	**40mg**	Oral	Daily on days 1 to 4
Peg-asparaginase	**2500units/m^2**	IV Infusion	Day 2

Maximum of 4 cycles (21 day cycle, assess response after a maximum of 2 courses)

Administration (+/- Counselling Points):

- **Co-trimoxazole and PPIs must be stopped at least 2 days prior to treatment**
- Piperacillin/Tazobactam (Tazocin®) should be avoided and meropenem used as first line treatment for febrile neutropenia following methotrexate infusion until methotrexate has cleared (level <0.1micromol/L)
- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.

- The hydration fluids on day 3 **MUST** start at least 6 hours prior to the methotrexate infusion.
- The patient's urine pH **MUST** be >7 before the methotrexate infusion is started.
- If urinary pH <7 during methotrexate infusion then additional sodium bicarbonate 8.4% 50mL can be infused separately by slow IV infusion (to be prescribed prn in Meditech).
- The second methotrexate infusion **MUST** start immediately after the loading dose.
- The blood sample needs to be sent to Alder Hey hospital in a taxi and then the lab at Alder Hey need to be rung for the result which should be documented in the medical notes.
- Folinic acid (calcium folinate) should be started 24 hours after the **start** of the methotrexate infusion
- The first methotrexate level should be taken 48 hours after the **start** of the methotrexate infusion. The methotrexate level should then be repeated daily until it is <0.1micromol/L at which point folinic acid rescue can stop.
- The dose of folinic acid (calcium folinate) may need to be modified 48 hours after the start of the methotrexate infusion in response to methotrexate levels (see High Dose Methotrexate Overview Protocol)
- If the serum creatinine increases by more than 25% from baseline then the folinic acid rescue should be escalated even before methotrexate level is known – seek urgent consultant advice.
- If severe methotrexate toxicity is suspected, then seek early consultant advice regarding the use of recombinant glucarpidase/carboxypeptidase.
- Patients should be monitored during and for one hour after Peg-asparaginase infusion.

Emetogenic risk

Moderately emetogenic

Supportive treatments:

High dose methotrexate pre-infusion medicines:

- Hydration fluids to start at least 6 hours before methotrexate

- Sodium bicarbonate 1g PO four times daily for 24 hours pre-methotrexate
- Sodium bicarbonate 8.4% IV 50mL slow IV bolus prn (to be used if urinary pH <7)

Supportive medicines:

- Allopurinol PO 100mg or 300mg daily (depending on renal function) for first cycle
- Aciclovir 400mg PO twice daily
- Famotidine 20mg twice daily (don't give PPI while on methotrexate)
- Filgrastim SC 30 or 48 million units daily days 3-10 of cycle
- Fluconazole PO 50mg daily
- Folinic acid IV 60mg every 6 hours to start 24 hours after the *start* of methotrexate infusion. See administration advice for further information.
- Ondansetron PO 8mg twice daily days 1 to 4.
- Pentamidine NEB 300mg every 28 days OR atovaquone liquid PO 750mg BD
- Chlorhexidine mouthwash 10ml twice daily

Suspend co-trimoxazole and routine folic acid until methotrexate level <0.1micromol/L

Extravasation risk:

Methotrexate: non-vesicant

Peg-asparaginase: non-vesicant

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

Dosing in renal and hepatic impairment:

A fluid space, e.g. pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. High dose methotrexate should not be given in such cases.

Methotrexate	
Renal, CrCl (ml/min) – use Wright equation	
>60	100% dose
40-60	50%
<40	Omit

Hepatic			
Bilirubin (micromol/L)		ALT (units/L)	Dose modification
<50	and	<180	100% dose
50-84	or	≥180	75% dose
≥85			Omit

Interactions:

Methotrexate – see High Dose Methotrexate Overview Protocol

Peg-asparaginase - use with caution alongside other hepatotoxic medication

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**IV hydration:** **1L sodium chloride 0.18% / glucose 4% containing 20mmol potassium chloride and 50ml 8.4%sodium bicarbonate (bicarbonate to be added on the ward)**		**IV**	Start infusion 6 hours prior to methotrexate infusion, run at a rate of 250ml/hr for 6 hours, then run at a rate of 125ml/hr for 3 hours 15 minutes concurrent with methotrexate infusions, then run at a rate of 250ml/hr until desired methotrexate level is achieved (<0.1microlmol/l)
	Methotrexate	**300mg/m^2**	**IV**	In 100mls sodium chloride 0.9% over 15 minutes. The patient's urinary pH MUST be >7 before starting the infusion.
	Methotrexate	**2700mg/m^2**	**IV**	In 1000mls of sodium chloride 0.9% over 3 hours.
1 to 4	**Dexamethasone**	**40mg**	**Oral**	
2	**Peg-asparaginase**	**2500units/ m^2**	**IV**	100ml sodium chloride 0.9% over 2 hours, patient should be monitored for infusion related reactions during infusion and for one hour post infusion

Main toxicities:

Methotrexate	Bone marrow suppression, mucositis, stomatitis, nausea, vomiting, diarrhoea, skin irritation/sensitivity, renal impairment, AKI, deranged LFTs, interstitial pneumonitis.
Peg-Asparaginase	Myelosuppression, febrile neutropenia, seizure, syncope, embolism, thrombosis, hepatotoxicity, diarrhoea

Glucarpidase – Methotrexate reversal agent

NHS England will fund glucarpidase as a reversal agent for methotrexate (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m^2)

- Who develop significant deterioration in renal function (>1.5x ULN and rising, or the presence of oliguria) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg

Refer to CCC glucarpidase protocol for further information

Investigations and treatment plan:

	Pre	All cycles day 1	All cycles Day 2	All cycles Day 3	Ongoing
Informed Consent	X				
Clinical Assessment	X	X			
SACT Assessment (including PS and toxicity assessment)	X	X	X		
FBC	X	X			
U&E & LFTs & Magnesium	X	X			
CrCl (Wright)	X	X			
PET/ CT scan	X				At the end of treatment and if clinically indicated
Bone marrow aspirate/ trephine	X				If clinically indicated
ECG/ ECHO					If clinically indicated
Methotrexate levels				X	Repeat daily until cleared
Weight	X	X			
Height	X				
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X				
Blood glucose	X	X			Repeat if clinically indicated
Clotting (PT/ APTT/ fibrinogen)	X	X			
Pregnancy test	X				If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle one can proceed if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Subsequent cycles can proceed if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

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 section entitled 'Dosing in Renal and Hepatic Impairment'

Peg-Asparaginase			
Toxicity	Grade 2	Grade 3	Grade 4
Hepato-toxicity	**Contra-indicated** if bilirubin >3x ULN or ALT >10 x ULN		
Hypersensitivity (e.g, urticaria, wheezing, laryngospasm, hypotension)	For urticaria **WITHOUT** bronchospasm, hypotension, edema or need for parenteral intervention, **CONTINUE** pegaspargase	For wheezing or other **SYMPTOMATIC** bronchospasm with or without urticaria, indicated parenteral intervention, angioedema or hypotension, **DISCONTINUE** pegaspargase	For life-threatening consequences or indicated urgent intervention, **DISCONTINUE** pegaspargase
Pancreatitis	For **ASYMPTOMATIC** amylase or lipase elevation **> 3x ULN** (chemical pancreatitis) or only radiological	For amylase or lipase elevation > 3x ULN until enzyme levels stabilise or are declining, **HOLD** pegaspargase	**PERMANENTLY DISCONTINUE** all pegaspargase for clinical pancreatitis (vomiting, severe abdominal pain)

	abnormalities, **CONTINUE** pegaspargase observe closely for rising amylase or lipase levels	For **SYMPTOMATIC** pancreatitis, **PERMANENTLY DISCONTINUE** pegaspargase	with amylase or lipase elevation > 3x ULN for more than 3 days and /or development of pancreatic pseudocyst
Hypertriglyceridemia	If triglyceride <11.3mmol/L**,** **CONTINUE** pegaspargase but follow closely for evolving pancreatitis	For triglyceride > 11.3mmol/L, **HOLD** pegaspargase ; follow closely for pancreatitis. After triglyceride level returns to normal range, **RESUME** pegaspargase at prior dose level.	
Hyperglycemia	For uncomplicated hyperglycemia, **CONTINUE** pegaspargase	For hyperglycemia requiring insulin therapy, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase at prior dose level.	For hyperglycemia with life-threatening consequences or indicated urgent intervention, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase and do not make up for missed doses
Hyperglycemia	For uncomplicated hyperglycemia, **CONTINUE** pegaspargase	For hyperglycemia requiring insulin therapy, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase at prior dose level.	For hyperglycemia with life-threatening consequences or indicated urgent intervention, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase and do not make up for missed doses
Hyperglycemia	For uncomplicated hyperglycemia, **CONTINUE** pegaspargase	For hyperglycemia requiring insulin therapy, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase at prior dose level.	For hyperglycemia with life-threatening consequences or indicated urgent intervention, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase and do not make up for missed doses
Hyperglycemia	For uncomplicated hyperglycemia, **CONTINUE** pegaspargase	For hyperglycemia requiring insulin therapy, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase at prior dose level.	For hyperglycemia with life-threatening consequences or indicated urgent intervention, **HOLD** pegaspargase until blood glucose regulated with insulin; resume pegaspargase and do not make up for missed doses

Non-CNS hemorrhage	For bleeding in conjunction with hypofibrinogenemia, **HOLD** pegaspargase until bleeding < Grade 1; **DO NOT HOLD** pegaspargase for abnormal laboratory findings **WITHOUT** a clinical correlate	**HOLD** pegaspargase until bleeding < Grade 1, acute toxicity and clinical signs resolved and coagulant replacement therapy stable or completed	
CNS thrombosis	For abnormal lab findings **WITHOUT** a clinical correlate, **CONTINUE** pegaspargase	**DISCONTINUE** all pegaspargase; if CNS symptoms and signs fully resolved and significant pegaspargase dose remains to be given, may resume at lower dose and/or longer intervals between doses	**PERMANENTLY DISCONTINUE** all pegaspargase
CNS hemorrhage	DISCONTINUE pegaspargase ; DO NOT withhold pegaspargase for abnormal lab findings WITHOUT a clinical correlate		

References:

1. https://www.medicines.org.uk/emc methotrexate (accessed March 2021)
2. https://www.medicines.org.uk/emc peg-asparaginase (accessed March 2021)
3. Thames Valley Strategic network MeAD protocol (Sept 2021)
4. Aintree Hospital NHS Trust MeAD protocol
5. BC Cancer Protocol Summary for Treatment of Refractory or relapsing extranodal Natural Killer or T-Cell lymphoma using Pegaspiraginase, Methotrexate and Dexamethasone (March 2018)

Circulation/Dissemination

Date added into Q-Pulse	17th August 2023
Date document posted on the Intranet	

Version History

		Author name and designation	Summary of main changes
		Dave Breen	New protocol
	2.0	**Jennifer Gibson**	**Transferred to new template.** **Removed requirement to stop methotrexate infusion after 3 hours.**