SA Health

Cancer Chemotherapy Protocol Registration Form and Template

SA Health Cancer Drug Committee

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Government of South Australia

SA Health

Applicant Details

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Supporting Specialist Pharmacist Details

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Supporting Specialist Nurse Details

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SA Health Cancer Drug Committee Use only:

Application received (date):	
Confirmation of costing confirmed* □	
Approval Status APPROVED □ Conditions of approval (if any): REJECTED □ Reason(s) for rejection:	
Treatment Risk Level allocated:	
SAH-CDC comments (if any)	
I acknowledge the application and to the best of my knowledge the information contained within is correct and confirm the decision made by the SA Health Cancer drug Committee in submitting this protocol to the SA Health Approved Cancer Chemotherapy Protocol Register: SAH-CDC Chair (or delegate):	Position:
Signature:	Date:

Protocol Name	
Protocol Number	

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CNS LYMPHOMA PROPHYLAXIS, R-MTX

Treatment Schedule - Summary

Drug	Dose	Route	Day
Rituximab	**375mg/m2**	**IV**	**1**
Methotrexate	**3500mg/m2**	**IV**	**1**
Calcium Folinate	**25mg**	**IV**	**2**
Pegfilgrastim	**6mg**	**subcut**	**Day of DC**
OR	***OR***		***OR***
Filgrastim	**5microg/kg**	**subcut**	**2**

Frequency: 14 days

Notes (*e.g. 1st line treatment, alternate scheduling options*):
To be given in between cycles of primary treatment for B-NHL, OR at the end of standard chemotherapy, depending on consultant preference, where the total number of rituximab containing chemotherapy cycles is no more than 8 cycles

Number of Cycles: usually 2; up to 4 in very high risk populations

Protocol

Indications and Patient Population: Prophylaxis of CNS lymphoma in CD20+ B-NHL patients considered at high risk of CNS disease as determined by location of lymphoma or CNS International Prognostic Index (CNS-IPI)

Indications for use: Advanced stage high-grade, CD20+ NHL with:
- CNS-IPI score ≥4
OR
- Significant extranodal disease, or with spinal, orbital, naso-pharyngeal, renal/adrenal, testicular involvement
OR
- 'Double-Hit' Lymphoma or Intravascular Lymphoma

Exclusions (*e.g. low GFR*): CrCL <30mL/min; severe hepatic impairment

Notes: Methotrexate is dose reduced as a proportion of CrCL/100 if CrCL <80mL/min (i.e if CrCL 75mL/min, 75% of methotrexate dose to be given)

Drug Status (PBS status, formulation etc.):

Rituximab is on the PBS for use with chemotherapy in induction or consolidation for CD20+ lymphoma (PBS streamline 7400) for up to 8 cycles. It is available as an IV formulation or subcutaneous fixed dose formulation.

Methotrexate is available on the general PBS schedule for doses up to 20g

Clinical Information:

Venous access requirements	Central access required (PICC preferred)
Supportive Care/ Premedication	Paracetamol 1g, cetirizine 10mg, dexamethasone 8mg po 60mins prior to rituximab Palonosetron 0.25mg IV 30 mins prior to methotrexate Dexamethasone 8mg on D2 and D3 Folinic acid rescue 25mg 6-hourly and sodium bicarbonate until MTX cleared in line with other methotrexate containing protocols
Hypersensitivity/infusion related reaction	Common with rituximab. However, as this protocol is designed to be given after at least 2 cycles of primary rituximab containing chemotherapy, risk of reaction should be significantly lower
Emetogenicity	Moderate
Drug reactions	Methotrexate induced AKI and delayed clearance
Blood tests	Hb, WCC, ANC, Plts, SeCr/CrCL, AST, bili, pH
Hepatitis B screening and prophylaxis	Required prior to starting If HBV SAg and/or Cab +ve, prophylaxis with entecavir required
Vaccinations	Live vaccines contraindicated – other vaccinations per the Immunisation Handbook or at clinician discretion
Effects of cancer treatment on fertility	High dose methotrexate has an effect on both male and female fertility during treatment, and is teratogenic. It is unlikely to affect fertility long-term.
Other:	Monitoring of methotrexate levels is essential as delayed methotrexate excretion is potentially an emergency situation. Methotrexate levels to be monitored every 24 hours until level is less than 0.05 micromol/L. Methotrexate is renally eliminated. Renal function must be evaluated prior to treatment. Methotrexate exits slowly from third space compartments (e.g. pleural effusions or ascites), resulting in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels. Glucarpidase is recommended in patients with high dose methotrexate (HDMTX)-induced acute kidney injury and delayed methotrexate clearance. It can rapidly lower methotrexate levels and early administration within 48 to 60 hours from the start of the HDMTX infusion is critical, as life-threatening toxicities may not be preventable beyond this time point

Treatment Schedule - Detailed

DAY 1

Drug	Dose	Administration/frequency
Paracetamol	1000mg PO	60 minutes before Rituximab
Cetrizine	10mg PO	60 minutes before Rituximab
Dexamethasone Tablets	8mg PO	60 minutes before Rituximab
Rituximab – in 500mL Sodium Chloride 0.9%	375mg/m^2 IV	Once only, as per graded administration rate guided by eviQ
Palonosetron	0.25mg IV Bolus	30 minutes before chemotherapy
PRE-HYDRATION: - Administer 100mL Sodium Bicarbonate 8.4% in 1000mL Sodium Chloride 0.9% over 4 hours - Continue hydration with Sodium Bicarbonate 8.4% as prescribed (Concurrent with Methotrexate infusion) - when urine pH is greater than 7, commence methotrexate.		
Methotrexate – in 1000mL Sodium Chloride 0.9%	3500mg/m^2 IV	Once only, over 2 hours
POST-HYDRATION: (To be charted on Sunrise or NIMC/fluid order) - Continue 100mL Sodium Bicarbonate 8.4% in 1000mL Sodium Chloride 0.9% over SIX to EIGHT hours consecutively, or as per consultant preference - Monitor urine pH and maintain >7 - Cease post-hydration when methotrexate level is less than 0.05micromol/L		

DAY 2->

Drug	Dose	Administration/frequency
Dexamethasone	8mg PO	Once a day with food on DAY 2 and DAY 3
Calcium Folinate (Leucovorin)	25mg IV Bolus	Over 1 to 2 minutes. Commence 24 hours after the start of MTX infusion and repeat every 6 hours until MTX level is <0.05micromol/L
Optional: Filgrastim **OR** Pegfilgrastim (Tick box option)	5microg/kg **OR** 6mg	Filgrastim – starting 24 hours after chemotherapy, and daily until ANC recovery Pegfilgrastim – once only on day of discharge (drop down box where prescriber can pick from D3,4,5,6 administration)

Frequency: 14 days

Number of Cycles: 2

Dose Modifications:

Haematological Toxicity

ANC <1 – delay until recovery

Platelets <100 – delay until recovery

Other: consider dose reduction or omission of C2 if significant or prolonged leukopenia or thrombocytopenia with C1

Renal Impairment

Contraindicated if creatinine clearance (mL/min): <30mL/min
If CrCL <80mL/min, dose as a proportion of CrCL. i.e if CrCL 75mL/min, give 75% of dose

Hepatic Impairment

Contraindicated in severe hepatic impairment

Mucositis and stomatitis

Grade 3 mucositis/stomatitis – reduce to 2g/m2; grade IV - withhold

Neurotoxicity

Nil

Other Toxicities

Use with caution in patients with significant third space fluid overload (eg. pleural effusions, ascites) due to altered methotrexate clearance. Drains or taps where necessary should be considered for these patients prior to high dose methotrexate

Interactions: As per eviQ protocols containing methotrexate or rituximab

Drug	Interaction	Clinical management
Rituximab + antihypertensives	Additive hypotensive effect	Consider withholding antihypertensive medications 12 hours prior to the rituximab infusion
Methotrexate + Ciprofloxacin, NSAIDS, Probenecid, Proton pump inhibitors	Increased toxicity of methotrexate possible due to reduced clearance	Combination contraindicated until MTX level <0.05micromol/L
Methotrexate + sulphonamides, penicillins	Increased toxicity of methotrexate possible due to displacement from serum protein binding	Avoid combination or monitor for methotrexate toxicity
Methotrexate + Trimethoprim	Increased toxicity of methotrexate possible due to additive antifolate	Avoid combination or monitor for methotrexate toxicity

	activity	
Methotrexate + Mercaptopurine	Increased toxicity of mercaptopurine possible due to reduced clearance	Avoid combination or monitor for mercaptopurine toxicity
Methotrexate + Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, cisplatin, contrast dye, frusemide)	Additive nephrotoxicity	Avoid combination or monitor renal function closely
Methotrexate + Hepatotoxic drugs (e.g. azathioprine, leflunomide, retinoids, sulfasalazine)	Additive hepatotoxicity	Avoid combination or monitor liver function closely
Methotrexate + folic acid (as in multivitamins)	Reduced efficacy of methotrexate possible due antagonism of its action	Avoid combination

General Interactions

	Interaction	**Clinical management**
As per eviQ		

Administration details

General patient assessment: See eviQ Antineoplastic Drug Patient Assessment Tool

Pre-treatment medications: as above

Chemotherapy - 🕛 Time out checklist

RITUXIMAB

Prior to administration:

Check baseline observations.
Check for previous adverse events during previous infusions.
Verify premedication has been taken. If not, administer 30 to 60 minutes prior to rituximab administration:
- paracetamol 1000 mg orally AND
- cetirizine 10 mg orally
- a steroid may also be included as a premed according to local guidelines

Initial infusion:

Commence rituximab infusion at 50 mg/hr for 30 minutes.
Repeat observations prior to each rate increase.
Increase rate by 50 mg/hr every 30 minutes, up to a maximum of 400 mg/hr if observations are stable.
Flush with ~ 100 mL of sodium chloride 0.9%.
If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer.

When symptoms have completely resolved, recommence the infusion at half the rate prior to the reaction.
For severe reactions stop infusion and manage as per emergency.
Transient hypotension may occur. Consider withholding antihypertensive medication for 12 hours before and during infusion.
Subsequent infusions:
If an adverse event was experienced with initial infusion recommence infusion at the same rate as initial infusion:
- commence rituximab infusion at 100 mg/hr
- repeat observations prior to each rate increase
- increase rate by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~ 100 mL of sodium chloride 0.9%
If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer.

When symptoms have resolved, recommence the infusion at half the rate prior to the reaction.
For severe reactions stop infusion and manage as per emergency.

METHOTREXATE INFUSION

Prehydration:
Administer 100 mL sodium bicarbonate 8.4% in 1000 mL glucose 5% OR sodium chloride 0.9% over 4 hours.
Continue hydration with sodium bicarbonate 8.4% as prescribed.
When urine pH is greater than 7 commence methotrexate.
If the urine pH drops below 7 during the methotrexate infusion administer stat dose of 100 mL sodium bicarbonate 8.4% over 15 minutes, continue to test all urine for pH, if the pH continues to drop below 7 seek medical review as further doses of sodium bicarbonate may be required.
Note: A large volume of intravenous fluid is given with this protocol if weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required)
Methotrexate:
Administer via IV infusion over 2 hours.
The starting time of the methotrexate infusion must be documented as the calcium folinate (leucovorin) rescue is to commence exactly 24 hours after the start of the methotrexate and continue until the methotrexate level is less than 0.05 micromol/L.
Flush with ~50 mL of sodium chloride 0.9%.
Post methotrexate:
Continue hydration with sodium bicarbonate 8.4% until methotrexate level is less than 0.05 micromol/L.
Continue to monitor all urine pH and fluid input and output.
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Note: Start calcium folinate (leucovorin) rescue 24 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.05 micromol/L.

Discharge Information
- Antiemetics as prescribed

- Growth factor support
- Prophylaxis medications (PJP prophylaxis, antivirals)
- Patient information

Monitoring

Tests/assessments	Frequency
Blood tests	
CBE, EUC, LFTs	Prior to each cycle and throughout cycle during admission
Methotrexate level	To commence 24 hours post methotrexate and continue every 24 hours until level is less than 0.05micromol/L

Side-effects

Immediate (onset hours to days)
Nausea/Vomiting, headache, hypotension, infusion reaction

Early (onset days to weeks)
Mucositis, diarrhoea, nephrotoxicity, hepatotoxicity, pancytopenia, skin rash/photosensitivity, arthralgia

Late (onset weeks to months)
Alopecia (10%), pulmonary toxicity, chemo fog

Supporting Documents

For more information

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