SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

R-CODOX-M / R-IVAC
BURKITT LYMPHOMA / DLBCL WITH ADVERSE FEATURES

PROTOCOL REF: MPHARCODO
(Version No. 1.0)

Approved for use in:

- Burkitt Lymphoma
- 'Double hit' or 'triple hit' lymphoma
- Diffuse large B-cell lymphoma (DLBCL) with adverse features

R-CODOX-M: Low risk patients give max. 3 cycles

R-CODOX-M / R-IVAC: High risk patients give R-CODOX-M / R-IVAC alternating for 4 cycles (2 cycles of each regimen)

Low Risk (must meet 3)	High Risk (must meet 2)
Normal lactate dehydrogenase (LDH) level	Raised LDH level
WHO performance status 0-1	WHO performance status 2-4
Ann Arbor stage I or II	Ann Arbor stage III or IV
No more than 1 extranodal site (e.g. bone marrow, gastrointestinal tract, or CNS)	More than 1 extranodal site

Blueteq not required

Dosage:

R-CODOX-M

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Days 1 of each treatment cycle
Cyclophosphamide	**800mg/m^2**	IV Infusion	Day 1 of each treatment cycle
Doxorubicin	**40mg/m^2**	IV Infusion	Day 1 of each treatment cycle
Vincristine	**1.5mg/m^2** (max 2mg)	IV infusion	Days 1 and 8 of each treatment cycle
Cyclophosphamide	**200mg/m^2**	IV infusion	Days 2-5 of each treatment cycle
Cytarabine	**70mg**	***Intrathecal***	Day 2 and 4
Methotrexate	**300mg/m^2** (100mg/m^2 if > 65 years)	IV infusion	Day 10 of each treatment cycle
Methotrexate	**2700mg/m^2** (900mg/m^2 if >65 years)	IV infusion	Day 10 of each treatment cycle
Filgrastim (Zarzio)	**48MU if >70kg/ 30MU if <70kg, daily**	Subcutaneous	Day 13 of each treatment cycle for 7 days
Methotrexate	**12.5mg**	***Intrathecal***	Day 15
Folinic acid	**15mg**	Oral	Day 16 (24 hours post intrathecal methotrexate)

If suspected/ proven CNS disease patients should receive two further intrathecals as shown below. Intrathecal days can be moved at clinician's discretion if logistical issues e.g. weekend.

Drug	Dose	Route	Frequency
Cytarabine	**70mg**	***Intrathecal***	Day 6 (cycle 1 R-CODOX-M only)
Methotrexate	**12.5mg**	***Intrathecal***	Day 17 (cycle 1 R-CODOX-M only) Prescribe 15mg folinic acid to be given 24 hours post intrathecal

R-IVAC

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1 of each treatment cycle
Etoposide	**60mg/m^2**	IV infusion	Days 1 to 5 of each treatment cycle
Mesna	**300mg/m^2** (200mg/m^2 if >65 years)	IV infusion	Days 1 to 5 of each treatment cycle
Ifosfamide	**1500mg/m^2** (1000mg/m^2 if >65 years)	IV infusion	Days 1 to 5 of each treatment cycle
Mesna	**1500mg/m^2** (1000mg/m^2 if >65 years)		
Mesna	**900mg/m^2**	IV infusion	Days 1 to 5 of each treatment cycle
Cytarabine	**2000mg/m^2** (1000mg/m^2 if > 65 years)	IV infusion	Days 1 and 2 **every 12 hours** of each treatment cycle (total of 4 doses)
Methotrexate	**12.5mg**	***Intrathecal***	Day 5
Folinic Acid	**15mg**	Oral	Day 6 (24 hours post intrathecal methotrexate)
Filgrastim (e.g. Zarzio®)	**48MU if >70kg/ 30MU if <70kg daily**	Subcutaneous	Day 7 of each treatment cycle until neutrophils >1.0x10^9/L for 2 consecutive days

If suspected/ proven CNS disease patients get two further intrathecals as shown below.

Intrathecal days can be moved at clinician's discretion if logistical issues e.g. weekend.

Drug	Dose	Route	Frequency
Cytarabine	**70mg**	***Intrathecal***	Day 7 and 9 (cycle 2 only i.e. 1st cycle of R-IVAC)

Administration:

Liaise with BMT team prior to initiation.

Methotrexate

- **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)
- The hydration fluids on day 10 **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.

Ifosfamide

- Ifosfamide can irritate the bladder mucosa. Patients should be encouraged to drink 3L of fluid per 24 hours. Test urine for microscopic haematuria every morning during each cycle as per urine testing protocol (see toxicity management)
- Administration of ifosfamide can cause CNS toxicity and other neurotoxic effects. Ifosfamide neurotoxicity may manifest within a few hours to a few days after first administration and in most cases resolves within 48 to 72 hours of ifosfamide discontinuation. Symptoms may persist for longer periods of time. Occasionally, recovery has been incomplete. Fatal outcome of CNS toxicity has been reported. Recurrence of CNS toxicity after several uneventful treatment courses has been reported. Methylene blue can be used to treat ifosfamide related encephalopathy. Observe for insidious signs of encephalopathy, initially somnolence and confusion (see toxicity management)

Contraception

- 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.
- Men should not father a child during the treatment and for a period of 6 months following discontinuation of the therapy
- Sexually active women and men should use effective methods of contraception during and after treatment is complete for these periods of time.

Emetogenic risk

Severely emetogenic - both R-CODOX-M & R-IVAC

Supportive treatments:

Rituximab pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Hydrocortisone sodium succinate IV bolus 100mg

High dose methotrexate pre-infusion medicines:

- Hydration fluids to start at least 6 hours before methotrexate
- Sodium bicarbonate 1g PO four times daily from 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 once daily (depending on renal function) for first cycle
- Aciclovir 400mg PO twice daily
- Chlorhexidine 0.2% mouthwash 10mLs twice daily
- Dexamethasone 4mg twice daily for 7 days (antiemetic)
- Famotidine 20mg twice daily (if on existing PPI therapy, not needed routinely)
- Filgrastim S/C 30 or 48 million units once daily (for 7 days starting on day 13 in RCODOXM and until neutrophil recovery starting day 7 in RIVAC) (30million units if <70kgs and 48 million units >70kgs).
- Fluconazole PO 50mg once daily
- Folinic acid IV 60mg every 6 hours to start 24 hours after the *start* of methotrexate infusion. See administration advice for further information.
- Metoclopramide PO 10mg three times daily prn
- Nystatin 1mL four times daily
- Ondansetron PO 8mg twice daily for 7 days
- Pentamidine NEB 300mg every 28 days OR atovaquone liquid PO 750mg twice daily
- Prednisolone 0.5% eye drops 1 drop into both eyes four times daily from day 1 to day 10 in R-IVAC only

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

Extravasation risk:

Rituximab/ Cyclophosphamide/ Cytarabine/ Methotrexate – Non vesicant

Etoposide/ Ifosfamide – Irritant

Doxorubicin/ Vincristine - 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 (mL/min) – use wright equation			
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

Cyclophosphamide

Renal Impairment (CrCl)		Hepatic Impairment
>20mL/min	100% of dose	SPC recommends a dose reduction but exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary – clinical decision
10-20mL/min	75% of dose	
<10mL/min	50% of dose	

Doxorubicin

Renal Impairment	Hepatic Impairment	
Clinical decision in severe renal impairment	AST 2-3 x ULN	75% dose
	Bilirubin 20-50µmol/L or AST >3x ULN	50% dose
	Bilirubin 51-85µmol/L	25% dose
	Bilirubin >85µmol/L	Omit

Vincristine

Renal Impairment	Hepatic Impairment	
No dose adjustments necessary	Bilirubin 26-51µmol/L or AST/ALT 60-180	50% dose
	Bilirubin >51µmol/L + normal AST/ALT	50% dose
	Bilirubin >51µmol/L + AST/ALT >180	Omit

Etoposide

Renal Impairment		Hepatic Impairment	
CrCl 15-50mL/min	75% of dose	Bilirubin ≥50µmol/L or decreased albumin	50% of dose
CrCl <15mL/min	50% of dose		

Ifosfamide

Renal Impairment		Hepatic Impairment	
GFR 40-59mL/min	70% of dose	Not recommended in patients with a Bilirubin >17µmol/L or serum transaminases or ALP >2.5 x ULN.	Clinical decision
GFR <40mL/min	Clinical decision		

Cytarabine

Renal Impairment		Hepatic Impairment
GFR 46-60	60% of dose	Bilirubin >34µmol/L give 50% of dose. Escalate doses in subsequent cycles in the absence of toxicity.
GFR 30-45	50% of dose	
GFR <30	Contraindicated	

Interactions:

Methotrexate – see High Dose Methotrexate Overview Protocol

Cytarabine

- Cytarabine may reduce digoxin levels. Digoxin level monitoring is recommended.
- An *in-vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. In patients on cytarabine being treated with gentamicin for a *K.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

Ifosfamide and etoposide

- Both possibly enhance the effect of warfarin. Close monitoring of INR is advised.
- Co-administration of anti-epileptics and etoposide can lead to a decrease in seizure control due to pharmacokinetic interactions.

Vincristine

- Mould active azoles (e.g. posaconazole) should be avoided in combination with vincristine as there is an increased risk of neurotoxicity. Fluconazole can be given but signs of neurotoxicity should be monitored.

- Vincristine may reduce levels of phenytoin and monitoring of phenytoin levels is recommended.

Doxorubicin

- Avoid concomitant cardiotoxic medication with anthracyclines (e.g. doxorubicin).
- Doxorubicin is metabolised via CYP450 enzymes and therefore caution should be exercised when using with strong CYP450 inhibitors and inducers.

Treatment schedule (R-CODOX-M)

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1000mg**	**PO**	30 minutes before rituximab
	Chlorphenamine	**10mg**	**IV**	30 minutes before rituximab
	Hydrocortisone	**100mg**	**IV**	30 minutes before rituximab
	Rituximab	**375mg/m^2**	**IV**	**Non-Hodgkin patients ONLY.** **≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline.
	Cyclophosphamide	**800mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
	Vincristine	**1.5mg/m^2** (max 2mg/dose)	**IV**	Sodium Chloride 0.9% 50mL over 5-10 minutes
	Doxorubicin	**40mg/m^2**	**IV**	Sodium Chloride 0.9% 100mL over 30 minutes
2	**Cyclophosphamide**	**200mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
	Cytarabine	**70mg**	***Intrathecal***	Refer to local intrathecal policy for further guidance
3	**Cyclophosphamide**	**200mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
4	**Cyclophosphamide**	**200mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
	Cytarabine	**70mg**	***Intrathecal***	Refer to local intrathecal policy for further guidance
5	**Cyclophosphamide**	**200mg/m^2**	**IV**	Sodium Chloride 0.9% 250mL over 30 minutes
8	**Vincristine**	**1.5mg/m^2** (max 2mg/dose)	**IV**	Sodium Chloride 0.9% 50mL over 5-10minutes
9	**Sodium bicarbonate**	**1g**	**PO**	QDS (start 24 hours prior to methotrexate and continue until methotrexate <0.1micromol/L)

10	**IV hydration: 1L sodium chloride 0.18% / glucose 4% containing 20mmol potassium chloride and 50mL 8.4%sodium bicarbonate (bicarbonate to be added at ward level)**		**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**	Sodium Chloride 0.9% 100mL over 15 minutes
	Methotrexate	**2700mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 3 hours
11	**Folinic Acid**	**60mg**	**IV**	Every 6 hours (start 24 hours after the start of methotrexate, continue until methotrexate level <0.1 micromol/L)
15	**Methotrexate**	**12.5mg**	***Intrathecal***	Refer to local intrathecal policy for further guidance
16	**Folinic Acid**	**15mg**	**PO**	Stat 24 hours after intrathecal methotrexate

Extra Intrathecal doses for CNS involvement:

Drug	Dose	Route	Frequency
Cytarabine	**70mg**	***Intrathecal***	Day 6 of **cycle 1 only**
Methotrexate	**12.5mg**	***Intrathecal***	Day 17 of **cycle 1 only**

Treatment schedule (R-IVAC):

Please note certain agents will run concurrently but through differing lumens of the central Hickman/PICC line

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1000mg**	**PO**	30 minutes before chemotherapy
	Chlorphenamine	**10mg**	**IV**	30 minutes before chemotherapy
	Hydrocortisone	**100mg**	**IV**	30 minutes before chemotherapy
	Rituximab	**375mg/m^2**	**IV**	**Non-Hodgkin patients ONLY.** **≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline.
	Etoposide	**60mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 1 hour
	Cytarabine	**2000mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL

				over 3 hours
	Mesna	**300mg/m^2**	**IV**	Sodium chloride 0.9% 100mL over 15 minutes
	Ifosfamide & Mesna	**1500mg/m^2 & 1500mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 1 hour
	Mesna	**900mg/m^2**	**IV**	Sodium chloride 0.9% 1000mL over 12 hours
	Cytarabine	**2000mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 3 hours
2	**Etoposide**	**60mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 1 hour
	Cytarabine	**2000mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 3 hours
	Mesna	**300mg/m^2**	**IV**	Sodium chloride 0.9% 100mL over 15 minutes
	Ifosfamide & Mesna	**1500mg/m^2 & 1500mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 1 hour
	Mesna	**900mg/m^2**	**IV**	Sodium chloride 0.9% 1000mL over 12 hours
	Cytarabine	**2000mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 3 hours
3	**Etoposide**	**60mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 1 hour
	Mesna	**300mg/m^2**	**IV**	Sodium chloride 0.9% 100mL over 15 minutes
	Ifosfamide & Mesna	**1500mg/m^2 & 1500mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 1 hour
	Mesna	**900mg/m^2**	**IV**	Sodium chloride 0.9% 1000mL over 12 hours
4	**Etoposide**	**60mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 1 hour
	Mesna	**300mg/m^2**	**IV**	Sodium chloride 0.9% 100mL over 15 minutes
	Ifosfamide & Mesna	**1500mg/m^2 & 1500mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 1 hour
	Mesna	**900mg/m^2**	**IV**	Sodium chloride 0.9% 1000mL over 12 hours
5	**Etoposide**	**60mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 1 hour
	Mesna	**300mg/m^2**	**IV**	Sodium chloride 0.9% 100mL over 15 minutes
	Ifosfamide & Mesna	**1500mg/m^2 & 1500mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 1 hour
	Mesna	**900mg/m^2**	**IV**	Sodium chloride 0.9% 1000mL over 12 hours

	Methotrexate	**12.5mg**	***Intrathecal***	Refer to local intrathecal policy for further guidance

Extra Intrathecal doses for CNS involvement

Drug	Dose	Route	Frequency
Cytarabine	**70mg**	***Intrathecal***	Days 7 and 9 of **cycle 1 only**

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea and infusion related reactions.

R-CODOX
Cyclophosphamide: Dysuria, haemorragic cystitis, taste disturbance Doxorubicin: Cardiomyopathy, alopecia, urinary discolouration Vincristine: Peripheral neuropathy, constipation, jaw pain
Methotrexate
Bone marrow suppression, mucositis, stomatitis, nausea, vomiting, diarrhoea, skin irritation/sensitivity, renal impairment, AKI, deranged LFTs, interstitial pneumonitis.
Ifosfamide
Haemorrhagic cystitis, encephalopathy, nephrotoxicity
Cytarabine
CNS toxicity, conjunctivitis, flu-like syndrome, pulmonary toxicity, GI toxicity
Etoposide
Hypotension on rapid infusion, hyperbilirubinaemia,

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	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Informed Consent	x					
Clinical Assessment	x				x	As clinically indicated or at the end of treatment
SACT Assessment (including PS and toxicity assessment)		x	x	x	x	
FBC	x	x	x	x	x	
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	x					
LDH	x					Repeat if clinically indicated
U&E & LFTs & bone profile	x	x	x	x	x	
CrCl (Wright formula)	x					
Urine dipstick for protein/ blood			x		x	See toxicity management
Radiological assessment	x					Repeat at the discretion of the MDT
ECG+/-ECHO	x					If clinically indicated
Observations (Blood pressure/ Pulse/ Temperature/ Respiratory rate)	x	x	x	x	x	Continuous monitoring required when on rituximab
Height	x					
Weight	x	x	x	x	x	Every cycle
Blood glucose	x					Repeat if clinically indicated
Serum pregnancy test	x					If clinically indicated
CSF examination (cell count+/- immunophenotype)	x					Can be done with first intrathecal

Dose Modifications and Toxicity Management:

Haematological toxicity:

No dose modifications are required for haematological toxicities.

Subsequent cycles can proceed if-

ANC ≥ 1.0 x 10^9/L	Unsupported platelets ≥ 75 x 10^9/L

Day 10 methotrexate can be given irrespective of neutrophil or platelet count.

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'

Peripheral Neuropathy

	Grade	Modification
Neurotoxicity	Grade 2 motor weakness or grade 3 sensory toxicity	Give 50% vincristine
	Higher grades of neurological toxicity	Omit vincristine
Elderly Population	Consider reducing the dose to 1mg for patients >70years old.	

Ifosfamide Induced Encephalopathy

Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately. Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass. Refer to Methylthioninium

Chloride (Methylene Blue) for Ifosfamide Induced Encephalopathy Clinical Guideline for more information.

Ifosfamide / Cyclophosphamide Induced Haemorrhagic Cystitis

Monitor closely for haematuria following cyclophosphamide (R-CODOX-M) and ifosfamide (R-IVAC) and inform consultant if this occurs.

Managing positive urine dip for blood

Test result	Action
Trace	Re-test
+	Re-test. If positive on more than one consecutive test give additional IV bolus mesna. Check fluids and any concurrent mesna is running correctly or oral dose has been taken.
++ / +++	Double dose of any concurrently running IV mesna. Repeated ++ / +++ result, or evidence of macroscopic haematuria should prompt pause and review of current treatment

Recommended bolus dose: Mesna intravenous 600mg/m^2 or a fixed dose of 1g in 250mL sodium chloride 0.9% over 30 minutes or oral mesna 1800mg. Patients needing bolus mesna should have their infusional mesna or oral doses doubled for all subsequent chemotherapy treatments.

Infusion Related Reactions:

Non-Haematological toxicities:	
Rituximab	
Infusion-related Reactions	Severe infusion-related reactions with fatal outcome can have an onset ranging within 30 minutes to 2 hours after starting the first rituximab infusion. They can be characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome (TLS) in addition to fever, chills, rigors, hypotension, urticaria, and angioedema. Severe cytokine release syndrome may occur. Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion

	should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis. Anaphylactic and other hypersensitivity reactions may occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms

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Version History

Date	Version	Author name and designation	Summary of main changes
April 2023	1.0	**Jennifer Gibson**	**New protocol**