SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Hyper-CVAD (+/-R) / MA (+/-R) AGGRESSIVE LYMPHOMA / ALL

PROTOCOL REF: MPHAHCVAD

Approved for use in:

- Patients with aggressive lymphoma or acute lymphoblastic leukaemia (ALL)

BLUETEQ NOT REQUIRED

Dosage Hyper-CVAD +/-R (Cycles 1, 3, 5, 7):

Drug	Dose	Route	Frequency
Methotrexate	**12.5mg**	INTRATHECAL	(Day 0)*
+/- Rituximab	**375mg/m^2**	IV infusion	Day 1 *(if CD20 positive)*
Mesna	**600mg/m^2**	IV infusion	Day 1, 2 and 3. To start one hour prior to cyclophosphamide infusion.
Cyclophosphamide	**300mg/m^2**	IV infusion	Twice daily on Day 1, 2 and 3
Dexamethasone	**40mg****	PO	Mane on days 1 to 4 and days 11 to 14
Doxorubicin	**50mg/m^2**	IV infusion	Day 4
Vincristine	**1.4mg/m^2 (max dose 2mg***)**	IV infusion	Day 4 and 11
Cytarabine	**70mg**	INTRATHECAL	Day 7

*can be given up to 4 days before Day 0

**Reduce dose to 20mg if elderly and unable to tolerate high dose steroid

***Consider capping at 1mg if >70 years old

Dosage MA +/-R (Cycles 2, 4, 6, 8):

Drug	Dose	Route	Frequency
Methotrexate	**12.5mg**	INTRATHECAL	Day 0*
+/- Rituximab	**375mg/m^2**	IV infusion	Day 0 *(if CD20 positive)*
Methotrexate	**1g/m^2**	IV infusion	Day 1
Cytarabine	****3g/m^2**	IV infusion	Day 2, 3 & 4 (24, 36, 48 and 60 hours after completion of methotrexate)
Methylprednisolone	**50mg**	IV infusion	BD on Days 1-3
Cytarabine	**70mg**	INTRATHECAL	Day 7

*can be given up to 4 days before Day 0

**Reduce dose to 1g/m^2 if >60 years old or significant co-morbidities

Maximum 4 cycles of R-Hyper-CVAD and 4 cycles of R-MA (alternating)

Administration:

- A dual lumen PICC is required
- 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.
- Doxorubicin hydrochloride may impart a red colour to the urine. Patients should be cautioned that this does not pose any health hazards.
- High dose cyclophosphamide may irritate the bladder. Encourage the patient to drink 3L per 24 hours (mesna is also administered to protect against this).

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

Rituximab pre-infusion medication:

- Paracetamol tablet 1gram oral (PO)
- Chlorphenamine injection 10mg intravenous (IV)
- HyperCVAD cycles: dexamethasone 40mg to be taken 30 minutes prior to rituximab
- RMA cycles: hydrocortisone injection 100mg intravenous (IV)

Supportive medication:

- Ondansetron 8mg twice daily (must take prior to chemotherapy doses)
- Metoclopramide 10mg three times a day when required.
- Allopurinol (dose based on renal function) for the first cycle.
- Docusate Sodium 200mg BD when required
- Famotidine 20mg twice daily (or PPI if needed following discussion with consultant)
- Aciclovir 400mg twice daily
- Consider PCP prophylaxis with pentamidine nebules 300mg via inhalation every 28 days (co-trimoxazole must not be given during treatment but should be given for 3 months following treatment)
- Chlorhexidine 0.2% mouthwash 10mL QDS prn
- Filgrastim (G-CSF, e.g. Zarzio) to start on day 5 and administer subcutaneously once daily until neutrophils are >1.0 x 10^9/L for 3 consecutive days
- ***Lymphoma Patients:*** Fluconazole 50mg PO daily
- ***Leukaemia Patients:*** Caspofungin (dose as per BNF) during hyperCVAD cycles. Switch to posaconazole 300mg TWICE daily for ONE day then 300mg ONCE daily on discharge (continue until ANC >1x10^9/L for 3 consecutive days)
- ***Leukaemia Patients:*** Consider ciprofloxacin 500mg twice daily in ALL (continue until ANC >1x10^9/L for 3 consecutive days)

Additional in R – MA cycles:

- Prednisolone 0.5% eye drops 1 drop into both eyes QDS from day 3 to day 10 of R-MA cycles only
- Nystatin 100,000units/mL 1mL QDS

Extravasation risk:

Rituximab: non-vesicant

Cyclophosphamide: non-vesicant

Doxorubicin: vesicant

Vincristine: vesicant

Methotrexate: non-vesicant

Cytarabine: non-vesicant

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

Interactions:

Doxorubicin

Caution required with drugs that cause cardiotoxicity or that affect cardiac function (e.g. trastuzumab or felodipine).

Ciclosporin increases the concentration of doxorubicin – monitor for toxicity.

Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels. Doxorubicin is a potent, radio sensitizing agent

Vincristine

Care needed with drugs that also cause neurotoxicity.

Vincristine may reduce plasma levels of phenytoin – monitor levels.

The following drugs decrease exposure to vincristine: phenobarbital, phenytoin and rifampicin.

The following drugs increase exposure to vincristine: amiodarone, macrolides, ciclosporin, letermovir, diltiazem, azole antifungals, aprepitant, ranolazine and verapamil or in patients with hepatic dysfunction.

Methotrexate

The following drugs should be avoided as they can reduce the clearance of methotrexate leading to increased toxicity: NSAIDs, diuretics, PPI's such as omeprazole and lansoprazole, co-trimoxazole, trimethoprim, penicillin's including Tazocin®.

Folic acid and vitamins containing folate should be avoided during methotrexate treatment as they can reduce the efficacy of treatment – continue at clinician discretion.

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity with intrathecal administration.

Methotrexate can reduce clearance of theophylline – monitor levels

Methotrexate increases plasma content of mercaptopurine – consider dose adjustement.

Cytarabine

Cytarabine may reduce digoxin levels. Digoxin level monitoring is recommended.

Treatment schedule (Hyper-CVAD +/-R):

Day	Time	Drug	Dose	Route	Diluent and rate
0*	TBC	Methotrexate	12.5mg	Intrathecal	
1	0900	Mesna	600mg/m^2	IV	In 1000mls Sodium Chloride 0.9% over 24 hours
	10:00	Cyclophosphamide	300mg/m^2	IV	In 250mls Sodium Chloride 0.9% over 2 hours. Start infusion 1 hour after mesna infusion has started.
	1200	Paracetamol	1g	PO	At least 30mins before rituximab
		Chlorphenamine	10mg	IV	
		Dexamethasone	40mg	PO	
	1230	Rituximab	375mg/m^2	IV	In 500mls Sodium Chloride 0.9%. See below for infusion rates.
	2200	Cyclophosphamide	300mg/m^2	IV	In 250mls Sodium Chloride 0.9% over 2 hours
2	09:00	Dexamethasone	40mg	PO	
	09:00	Mesna	600mg/m^2	IV	In 1000mls Sodium Chloride 0.9% over 24 hours
	10:00	Cyclophosphamide	300mg/m^2	IV	In 250mls Sodium Chloride 0.9% over 2 hours.
	2200	Cyclophosphamide	300mg/m^2	IV	In 250mls Sodium Chloride 0.9% over 2 hours
3	09:00	Dexamethasone	40mg	PO	
	09:00	Mesna	600mg/m^2	IV	In 1000mls Sodium Chloride 0.9% over 24 hours

	10:00	Cyclophosphamide	300mg/m^2	IV	In 250mls Sodium Chloride 0.9% over 2 hours.
	2200	Cyclophosphamide	300mg/m^2	IV	In 250mls Sodium Chloride 0.9% over 2 hours
4	09:00	Dexamethasone	40mg	PO	
	10:00	Doxorubicin	50mg/m^2	IV	In 100ml Sodium Chloride 0.9% over 24 hours
	11:00	Vincristine	1.4mg/m^2 (max 2mg dose)	IV	In 50ml Sodium Chloride 0.9% over 10 minutes
5	0900	Filgrastim	30 or 48 million units	S/C	Dose depends on weight. Continue until ANC > 1.0 x 10^9/L for 3 consecutive days.
7	TBC	Cytarabine	70mg	Intrathecal	
11	0900	Dexamethasone	40mg	PO	
	1000	Vincristine	1.4mg/m^2 (max 2mg dose)	IV	In 50ml Sodium Chloride 0.9% over 10 minutes
12 to14	0900	Dexamethasone	40mg	PO	

*can be given up to 4 days before Day 0

Treatment schedule (MA +/-R):

Day	Time	Drug	Dose	Route	Diluent and rate
0*	TBC	Methotrexate	12.5mg	Intrathecal	
0	0900	Paracetamol	1g	PO	At least 30mins before rituximab
		Chlorphenamine	10mg	IV	
		Hydrocortisone	100mg	IV	
	09:30	Rituximab	375mg/m^2	IV	In 500mls Sodium Chloride 0.9%. See below for infusion rates.
1	06:00	Methylprednisolone	50mg	IV	In 100ml Sodium Chloride 0.9% over 30 minutes
	08:00	IV hydration – see supplementary fluid prescription		IV	Start at least 6 hours prior to methotrexate. Continue until methotrexate level is <0.1micromol/L
	14:00	Methylprednisolone	50mg	IV	In 100ml Sodium Chloride 0.9% over 30 minutes

	15:00	Methotrexate	1g/m^2	IV	In 500mls Sodium Chloride 0.9% over 3 hours
2	06:00	Methylprednisolone	50mg	IV	In 100ml Sodium Chloride 0.9% over 30 minutes
	15:00	Folinic acid	60mg	IV	Every 6 hours until methotrexate level is less than 0.1micromol/L.
	14:00	Methylprednisolone	50mg	IV	In 100ml Sodium Chloride 0.9% over 30 minutes
	18:00	Cytarabine	3g/m^2	IV	In 500mls of Sodium Chloride 0.9% over 2 hours
3	06:00	Cytarabine	3g/m^2	IV	In 500mls of Sodium Chloride 0.9% over 2 hours
	06:00	Methylprednisolone	50mg	IV	In 100ml Sodium Chloride 0.9% over 30 minutes
	14:00	Methylprednisolone	50mg	IV	In 100ml Sodium Chloride 0.9% over 30 minutes
	18:00	Cytarabine	3g/m^2	IV	In 500mls of Sodium Chloride 0.9% over 2 hours
4	06:00	Cytarabine	3g/m^2	IV	In 500mls of Sodium Chloride 0.9% over 2 hours
5	0900	Filgrastim	30 or 48 million units	s/c	Continue until neutrophils are >1.0 x 10^9/L for 3 consecutive days
7	TBC	Cytarabine	70mg	Intrathecal	

*can be given up to 4 days before Day 0

High Dose Methotrexate Protocol:

Pre-Hydration:

Hydration MUST start at least 6 hours prior to the methotrexate infusion and run continuously until methotrexate level <0.1micromol/L. See pre-printed hydration fluid chart.

Urinary pH:

Urinary pH MUST be checked prior to starting methotrexate infusion and during the infusion. If a pH of >7 is not achieved with the standard hydration fluid then increase the amount of sodium bicarbonate 8.4% added to the hydration fluid to 100mls per 1L.

Methotrexate Blood Levels:

The first methotrexate level should be taken 48 hours after the start of the methotrexate infusion. The methotrexate level should be repeated every 24 hours until it is <0.1micromol/L at which point folinic acid rescue can stop.

The blood sample needs to be taxied to Alder Hey hospital and then the lab at Alder Hey need to be rung for the result which should be documented in the medical notes.

Calcium Folinate (Folinic Acid) Rescue:

Folinic acid (calcium folinate) 60mg IV every 6 hours should be started 24 hours after the start of the methotrexate infusion without delay. The dose of calcium folinate (folinic acid) should be modified 48 hours after the start of the methotrexate infusion as follows:

Methotrexate Level (micromol / L)	Calcium Folinate Dose
<0.3	30mg oral every 6 hours
0.3 – 0.5	60mg IV every 6 hours
0.5 – 0.9	100mg/m^2 IV every 6 hours
≥ 1.0	200mg/m^2 IV every 6 hours

*Oral can only be given if the patient is compliant and not vomiting

If the serum creatinine increases by more than 25% from baseline then the folinic acid rescue should be escalated even before MTX level is known – seek urgent consultant advice.

If severe MTX toxicity is suspected, then seek early consultant advice regarding the use of recombinant glucarpidase/carboxypeptidase.

Cyclophosphamide associated Haemhorragic Cystitis (Haematuria)

Patients must have their urine tested twice daily on each day of Hyper CVAD treatment cycles for microscopic haematuria using Medi-Test Combi 8 strips. This is because high dose cyclophosphamide is can cause haehorrhagic cystitis. Mesna is prescribed alongside the cyclophosphamide within this protocol to protect against this. There is limited evidence that mesna will resolve haematuria once it occurs, however continued administration may prevent worsening and will not cause harm to the patient.

In the event of a positive urine test or haematuria:

- Contact a Haemato-oncology Consultant to review the cyclophosphamide infusion
- An additional dose of **Mesna 1g IV bolus over 5 minutes stat** should be considered in the event of haematuria and repeated at clinician discretion.

Main toxicities:

All regimens: Bone marrow suppression (thrombocytopenia, neutropenia, anaemia), nausea, vomiting, diarrhoea,

R-Hyper-CVAD: Cyclophosphamide can cause haemorrhagic cystitis, doxorubicin is cardiotoxic, vincristine is neurotoxic and rituximab can cause cytokine release syndrome.

R-MA: Methotrexate can cause severe mucositis, stomatitis, hepatic and renal impairment. Cytarabine has been linked to corneal toxicity.

Rituximab Infusion Related Reactions:

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

Investigations and treatment plan:

	Pre	Prior to each R- Hyper CVAD	Day 1 to 4 Hyper-CVAD	Prior to each R-MA	48 hrs after START of methotrexate	72 hrs after START of methotrexate + every 24 hours thereafter	Ongoing
Informed Consent	X						
Clinical Assessment	X	X		X			As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X		X			Prior to each cycle and each day of treatment as appropriate
Hepatitis BsAG and core antibody and viral screen	X						Include Hep C, HIV, EBV, CMV, VZV
FBC	X	X	X	X	X	X	Daily whilst an inpatient and as clinically indicated in between cycles
U&E & LFTs & Magnesium	X	X	X	X	X	X	Daily whilst an inpatient and as clinically indicated in between cycles
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	Use Wright's formula if borderline
CT scan	X						After cycle 4 and at the end of treatment and if clinically indicated
ECG	X						If clinically indicated
Blood pressure measurement	X			X			Repeat if clinically indicated
Urine dipstick for haematuria		X	X				Twice daily
Methotrexate level					X	X	If clinically indicated
Height and Weight recorded	X	X		X		X	Every cycle
Blood glucose	X						Repeat if clinically indicated
Fluid balance / urine output				X	X	X	Check 4 hourly during methotrexate treatment and as indicated
Pregnancy test	X						As appropriate
Fertility Preservation	X						As appropriate

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed if-

ANC > 1.0 x 10^9/L	Platelets > 60 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:

Dosing in renal and hepatic impairment:

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="2">Hepatic Impairment</th></tr>
<tr><td rowspan="4">Cyclophosphamide</td><td>CrCl (ml/min)</td><td>Modification</td><td colspan="2" rowspan="4">No dose adjustment necessary</td></tr>
<tr><td>>20</td><td>100%</td></tr>
<tr><td>10-20</td><td>75%</td></tr>
<tr><td><10</td><td>50%</td></tr>
<tr><td rowspan="4">Doxorubicin</td><td colspan="2" rowspan="4">No dose adjustment necessary</td><td>Parameter</td><td>Modification</td></tr>
<tr><td>AST 2-3 x ULN</td><td>75%</td></tr>
<tr><td>Bilirubin 21-50
or
AST >3 x ULN</td><td>50%</td></tr>
<tr><td>Bilirubin 51-85</td><td>25%</td></tr>
<tr><td rowspan="4">Vincristine</td><td colspan="2" rowspan="4">No dose adjustment necessary</td><td>Parameter</td><td>Modification</td></tr>
<tr><td>Bilirubin 26-51
or
AST/ALT 60-180</td><td>50%</td></tr>
<tr><td>Bilirubin >51
and
AST/ALT normal</td><td>50%</td></tr>
<tr><td>Bilirubin >51
and
AST/ALT >180</td><td>Omit</td></tr>
<tr><td>Methotrexate</td><td>CrCl (ml/min)</td><td>Modification</td><td>Parameter</td><td>Modification</td></tr>
</table>

	46 - 60	65% dose	Bilirubin 51 – 85 **Or** AST>180	75% dose
	30 - 45	50% dose	Bilirubin >85	Omit – clinical decision
	<30	Omit	HDMTX can can cause raised transaminases and hyperbilirubinemia lasting up to 2 weeks. Discontinue methotrexate if persists longer than 3 weeks	
Cytarabine	**CrCl (ml/min)**	**Modification**	**Parameter**	**Modification**
	46 - 60	60% dose	Bilirubin >34	50% dose
	30 - 45	50% dose	Escalate dose in subsequent cycles in the absence of toxicity	
	<30	Omit		

Neurotoxicity:

Vincristine		
Neurotoxicity	**Grade**	**Modification**
	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.	

References:

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4. Thomas DA, Cortes J, O'Brien S, Pierce S, Faderl S, Albitar M, et al. Hyper-CVAD program in Burkitt'stype adult acute lymphoblastic leukemia. J Clin Oncol. 1999 Aug;17(8):2461-70.
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6. Romaguera JE, Fayad L, Rodriguez MA, Broglio KR, Hagemeister FB, Pro B, et al. High rate of durable remissions after treatment of newly diagnosed aggressive mantle-cell lymphoma with rituximab plus hyper-CVAD alternating with rituximab plus high-dose methotrexate and cytarabine. J Clin Oncol. 2005 Oct 1;23(28):7013-23.
7. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006 Apr 1;106(7):1569-80.
8. O'Brien S, Thomas DA, Ravandi F, Faderl S, Pierce S, Kantarjian H. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. Cancer. 2008 Oct 15;113(8):2097-101.
9. 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.

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
July 2022	1.0	**Jennifer Gibson** **Principal Pharmacist Haemato-oncology**	V1.0 New regimen protocol