SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Induction Phase 1 (25 – 60 years) Acute Lymphoblastic Leukaemia (ALL)

PROTOCOL REF: MPHAIND
(Version No. 1.1)

Approved for use in:

Induction of remission in ALL in patients suitable for intensive treatment.

This protocol is suitable for patients aged 25-60 years. It may sometimes be used in older patients ≤ 65 years or in patients ≥ 19 years with Philadelphia Chromosome positive ALL. Follow MDT recommendation.

Blueteq is not required

Dosage:

Pre-Phase Steroids

Drug	Dose	Route	Frequency
Dexamethasone	**6 mg/m^2**	Oral	Daily for 5 to 7 days

Phase 1 Philadelphia Negative

Drug	Dose	Route	Frequency
Daunorubicin	**30mg/m^2**	IV	Days 1, 8, 15 and 22
Vincristine	**1.4 mg/m^2** (max 2mg)	IV	Days 1, 8, 15 and 22
Rituximab	**375mg/m^2**	IV	Days 3 and 10 **(CD20+ disease only)**
Dexamethasone	**10 mg/m^2** (max 20mg)	Oral	Days 1 to 4, 8 to 11 and 15 to 18
Peg-aspargase* (Oncaspar®)	**1000 IU/m^2**	IV	Day 4 and 18 (Omit on day 4 if ≥41 years old)
Methotrexate**	**12.5mg**	Intrathecal	Day 14

*Peg-aspargase (Oncaspar®) is only NICE approved for untreated ALL

Single Cycle

Phase 1 Philadelphia Positive

Drug	Dose	Route	Frequency
Daunorubicin	**30mg/m^2**	IV	Days 1, 8, 15 and 22
Vincristine	**1.4 mg/m^2** (max 2mg)	IV	Days 1, 8, 15 and 22
Rituximab	**375mg/m^2**	IV	Days 3 and 10 **(CD20+ disease only)**
Dexamethasone	**10 mg/m^2** (max 20mg)	Oral	Days 1 to 4, 8 to 11 and 15 to 18
Methotrexate**	**12.5mg**	Intrathecal	Day 14
Imatinib (only in Philadelphia positive ALL)	**400mg**	Oral	Daily continuously (aim to escalate to 600mg daily within 2 weeks if tolerated, continue until transplant)

Single Cycle

** Timing of Intrathecal therapy can be moved +/- 3 days to allow administration on specified lists as per local guidance. In the case of traumatic lumbar puncture (>10 red blood cells per microlitre), patients should be treated as having CNS disease IF they still have blasts within the peripheral blood at the time of occurrence or have blasts in the CSF. In this case and in the case where there is existing evidence of established CNS disease, intrathecal therapy with methotrexate should be escalated to twice per week and given at this frequency until the cytospin is clear of blasts. Such patients should also receive cranial irradiation, prior to consolidation, if they are not going to receive myeloablative allogeneic transplant.

Administration:

- Unless urgent clinical need precludes insertion, should be given via central line
- Patients will need admitting for therapy
- Possible life threatening anaphylaxis and anaphylactoid reactions can occur with peg-aspargase (Oncaspar®). 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 (Oncaspar®) can cause fluctuations in coagulation factors – monitor closely for signs of bleeding/clots.
- Contraceptive advice –males must use effective contraceptive measures during and for up to 6 months following treatment.
- 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 receive counselling on sperm conservation before start of daunorubicin treatment because of the possibility of irreversible infertility.
- For women who want to become pregnant after completing daunorubicin treatment, genetic counselling is also recommended.
- Daunorubicin hydrochloride causes episodes of nausea and vomiting, which sometimes can lead to impairment of the ability to drive or use machines.
- Special caution should be exercised in patients with preceding, concurrent or planned radiotherapy. These patients have an increased risk of local reactions in the radiation area (recall phenomena) during treatment with daunorubicin hydrochloride. Discuss with consultant.
- Anthracyclines should be avoided in patients with arrhythmias, recent myocardial infarction or myocardial insufficiency – discuss with consultant.
- Imatinib should be administered orally with a meal and a large glass of water to minimise the risk of gastrointestinal irritations.

Post Induction (Phase 1) Bone Marrow Monitoring

Following Phase 1 recovery (ANC > 0.75 x 10^9/L and Platelet > 75 x 10^9/L), remission should be confirmed by morphological bone marrow examination done by Day 35 at the latest. However, progression to Phase 2 should not be delayed more than a few days once haematopoietic recovery has occurred. If the patient is not in CR at the end of Phase 1, swift progression to Phase 2 treatment is indicated. If count recovery is not achieved by Day 35, the bone marrow aspirate should still be done to check whether non-recovery is due to residual

disease. If the Day 35 marrow is hypocellular with no recovering haematopoiesis or signs of relapsed or residual ALL, it is appropriate to wait a week and repeat the marrow as clinically indicated and to send any subsequent, more cellular specimens for MRD analysis.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

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

Supportive Medications:

- **Ensure oral chemotherapy (imatinib if appropriate) and steroids prescribed on inpatient account as appropriate**
- Allopurinol 300mg daily for 28 days (first cycle only). Consider rasburicase and IV hydration in patients at high risk of tumour lysis syndrome
- Aciclovir 400mg twice daily
- Liposomal Amphotericin B (AmBisome®) 7mg/Kg weekly OR 1mg/Kg daily in 500mL glucose 5% over 2 hours. Aim to start between day 4 to 7. Avoid azole antifungals 72 hours before or after vincristine
- Co-trimoxazole 960mg twice daily on 2 days per week (monthly nebulised pentamidine is an alternative if needed)
- Metoclopramide 10mg three times daily prn
- Norethisterone 5mg three times daily until platelets >50 $x10^9$/L with recovery (menstruating women only)
- Omeprazole 20mg once daily whilst on steroids, review once completed.
- Ondansetron 8mg twice daily oral on days 1, 8, 15 and 22

The following can be added clinician discretion if needed:

- Ciprofloxacin 500mg twice daily (until neutrophils >1.0x10^9/L for 2 consecutive days)
- Chlorhexidine 0.2% mouthwash 10mL four times daily
- Nystatin 1mL four times daily

Extravasation risk:

Rituximab: Non- vesicant

Daunorubicin: Vesicant

Vincristine: Vesicant

Peg-aspargase: Non-vesicant

Methotrexate: Irritant

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

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
Drug	**Creatinine clearance (mL/min)**	**Dose modification**
Daunorubicin	30 – 50	75% dose
	<30	50% dose
Vincristine	No dose adjustment required	
Peg-aspargase (Oncaspar®)	No dose adjustment necessary	
Imatinib	Use with caution. Reduce dose if not tolerated. Increase dose if lack of efficacy	
Rituximab	No dose adjustment necessary	

Hepatic Dose Modifications		
Drug	**Bilirubin (µmol/L)**	**Dosing**
Daunorubicin	50 – 89	50% dose
	90 - 119	25% dose
	≥120	Omit
	Do not alter dose for abnormal transaminases	
Vincristine	25 to 50	50% dose
	>50	Omit
	Do not alter dose for abnormal transaminases. Consider continuing full dose if Gilbert's syndrome at clinician discretion.	

Peg-aspargase (Oncaspar®)	>50	Omit
	Because of the risk of severe liver toxicity, liver function tests should be performed regularly. Do not alter for abnormal transaminases.	
Imatinib	Dose reduce if not tolerated. If Bilirubin > 3 x ULN or Liver transaminases > 5 x ULN, withhold until Bilirubin < 1.5 x ULN and Liver transaminase < 2.5 x ULN. Resume at reduced dose: 400mg to 300mg; 600mg to 400mg Consider alternative TKI at clinician discretion ie ponatinib	
Rituximab	No dose adjustment necessary	

Interactions:

Daunorubicin

- Ciclosporin - Increased concentration of daunorubicin and risk of toxicity
- Increased risk of cardiac toxicity when given with other cardiotoxic drugs such as trastuzumab

Vincristine

- Care is needed with concurrent drugs that can also cause neurotoxicity.
- Vincristine may reduce plasma levels of phenytoin therefore dose adjustment of phenytoin based on levels may be required.
- Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction.
- When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vincristine should be delayed until radiation therapy has been completed.
- Avoid azole antifungals for 72 hours before or after vincristine due to increased risk of neurotoxicity. Liposomal Amphotericin B is recommended as alternative in this protocol.

Peg-aspargase (Oncaspar®)

- Concomitant use of warfarin, heparin, dipyridamole, acetylsalicylic acid or non-steroidal anti-inflammatory should be done with caution due to changes in coagulation factors
- Vincristine should not be given on the same day as peg-aspargase

- Methotrexate and cytarabine can interact differently with Oncaspar®: their prior administration can increase the action of peg-aspargase synergistically. If these substances are given subsequently, the effect of peg-aspargase can be weakened antagonistically.
- Peg-aspargase 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.

Imatinib

- Increased risk of hepatotoxicity when given with peg-aspargase (Oncaspar®)
- Imatinib may inhibit CYP3A4 and so caution is recommended when administering with CYP3A4 substrates with a narrow therapeutic window (e.g. ciclosporin, pimozide, tacrolimus, sirolimus, ergotamine, diergotamine, fentanyl, alfentanil, terfenadine, bortezomib, docetaxel and quinidine). Imatinib may increase plasma concentration of other CYP3A4 metabolised medicinal products (e.g. triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, i.e. statins, etc.).

Please refer to the SPC for full list of interactions and further information.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
	Daunorubicin	**30mg/m^2**	**IV**	In 100mL sodium chloride 0.9% over 60 minutes
	Vincristine	**1.4 mg/m^2 (max 2mg)**	**IV** *Fatal by any other route*	In 50mL sodium chloride 0.9% over 15 minutes
2	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
3	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	30 minutes before rituximab
	Chlorphenamine	**10mg**	**IV**	30 minutes before rituximab
	Paracetamol	**1g**	**Oral**	30 minutes before rituximab
	Rituximab	**375mg/m^2**	**IV**	**≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9%

				Rate as per rituximab infusion guideline.
4	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
	Peg-aspargase (Oncaspar®) (Omit if Ph+ve or ≥41 years old)	**1000 IU/m^2**	**IV**	In 100mL sodium chloride 0.9% over 2 hours into side arm of fast flowing infusion
8	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
	Daunorubicin	**30mg/m^2**	**IV**	In 100mL sodium chloride 0.9% over 60 minutes
	Vincristine	**1.4 mg/m^2 (max 2mg)**	**IV** *Fatal by any other route*	In 50mL sodium chloride 0.9% over 15 minutes
9	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
10	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	30 minutes before rituximab
	Chlorphenamine	**10mg**	**IV**	30 minutes before rituximab
	Paracetamol	**1g**	**Oral**	30 minutes before rituximab
	Rituximab	**375mg/m^2**	**IV**	**≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline.
11	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
14	**Intrathecal below to be given each cycle as per Intrathecal Policy**			
	Methotrexate	**12.5mg**	**Intrathecal**	As per Intrathecal Policy
15	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
	Daunorubicin	**30mg/m^2**	**IV**	In 100mL sodium chloride 0.9% over 60 minutes
	Vincristine	**1.4 mg/m^2 (max 2mg)**	**IV Infusion** *Fatal by any other route*	In 50mL sodium chloride 0.9% over 15 minutes
16	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
17	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane
18	**Dexamethasone**	**10mg/m^2** (max 20mg)	**Oral**	Mane

	Peg-aspargase (Oncaspar®) (Omit if Ph+ve)	**1000 IU/m^2**	**IV**	In 100mL sodium chloride 0.9% over 2 hours into side arm of fast flowing infusion
22	**Daunorubicin**	**30mg/m^2**	**IV**	In 100mL sodium chloride 0.9% over 60 minutes
	Vincristine	**1.4 mg/m^2 (max 2mg)**	**IV Infusion** *Fatal by any other route*	In 50mL sodium chloride 0.9% over 15 minutes

Main toxicities:

Daunorubicin
Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), cardiotoxicity, alopecia, discolouration of the urine, infection, deranged LFTs
Vincristine
Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), neurotoxicity, constipation, peripheral neuropathy, deranged LFTs
Peg-aspargase (Oncaspar®)
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.
Imatinib
Neutropenia, thrombocytopenia, anaemia, hepatotoxicity, headache, nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, fluid retention, dermatitis, muscle spasm and cramps, musculoskeletal pain. Reactivation of HBV has also been reported.
Rituximab
Infusion reactions, cytokine release syndrome, hepatitis B reactivation

Investigations and treatment plan:

	Before Treatment	Day 1	Day 8	Day 15	Day 22	Ongoing
Informed Consent	X					
Clinical Assessment. Performance status recorded.	X	X				Before treatment and prior to every cycle
Observations (Blood pressure/ Pulse/ Temperature/ Respiratory rate)	X	X	x	x	x	Daily during treatment
FBC, U&E and LFTs, bone profile, CrCl	X	X	x	x	x	Monitor regularly throughout treatment
Amylase, clotting screen, fibrinogen, glucose, ammonia	x	x	x	x	x	Monitor regularly during treatment with peg-aspargase
ECHO/MUGA and ECG	X					ECG /ECHO for all patients should be documented before starting anthracycline, unless stated by the medical team that this is not required
TMPT genotype	x					Prior to treatment.
Bone Marrow	X					Before treatment and before Phase 2
B2Microglobulin	X					Before treatment
Virology (Hepatitis B/C serology, HIV)	X					Before treatment
Pregnancy test	X					As appropriate
Height	X					
Weight	X	X				
Imaging as per NICE/network guidance and clinical indication	X					Before treatment and to restage as indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

No dose modifications required for haematological parameters.

Non- Haematological toxicity:

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

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.	

Pancreatic effects (Peg-aspargase (Oncaspar®))

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

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.

References:

1. https://www.medicines.org.uk/emc Vincristine
2. https://www.medicines.org.uk/emc Daunorubicin
3. https://www.medicines.org.uk/emc Peg-aspargase (Oncaspar®)
4. UKALL14. A randomized trial for adults with newly diagnosed acute lymphoblastic leukaemia. Eudract No: 2009-012717-22. Version 12.0, 26.06.2018.
5. 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

6. Clinical Commissioning Policy: Addition of rituximab to first-line standard chemotherapy for CD20 positive B-cell precursor acute lymphoblastic leukaemia (Adults) v1.0. January 2021. https://www.england.nhs.uk/wp-content/uploads/2021/01/1748-Addition-of-rituximab-to-first-line-standard-chemotherapy-for-CD20-positive-B-cell-precursor-acute-lympho.pdf

Circulation/Dissemination

Date added into Q-Pulse	26th January 2024
Date document posted on the Intranet	

Version History

Date	Version	Author name and designation	Summary of main changes
Aug 2023	1.0	**Jennifer Gibson – Principal Pharmacist HO**	**New Protocol**
October 2023	1.1	**Sophie Hughes – Advanced Pharmacist**	**ECHO/ECG updated re anthracycline guidance**