ALL Phase 1 Induction (25-60 years)

INDICATION
Induction of remission in Adult Acute Lymphoblastic Leukaemia (ALL) patients

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 acute lymphoblastic leukaemia. Follow MDT recommendation.

TREATMENT INTENT

Achieving complete remission

PRE-ASSESSMENT

1. Blood tests - FBC, coagulation screen, DAT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, $\beta_2$microglobulin, Hepatitis B core antibody and Hepatitis BsAg, Hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, group and save, HTLV 1+2, TPHA, toxoplasma +/-HSV, Syphilis serology
2. Bone marrow aspirate and trephine
3. Confirm disease diagnosis from bone marrow aspirate (or peripheral blood where there is high presenting WCC) using immunophenotyping / flow cytometry
4. Confirmation of the presence of t(9;22) and/or BCR-ABL transcript
5. Cytogenetic, FISH and molecular genetic analysis on a pre-treatment bone marrow
6. If any suspicion of neurological disease: MRI head/spine, perform Lumber puncture
7. Tissue typing of patient and any siblings to be carried out. Donor search to be initiated if no matched sibling donor available.
8. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women aged 12 – 55 years of age unless they have been sterilised or undergone a hysterectomy
9. ECG +/- Echo
10. Record performance status (WHO/ECOG)
11. Record height and weight (also needed to calculate CrCl)
12. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment
13. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see Fertility Guidelines)
14. Hydration - in patients with bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol
15. Consider dental assessment / advise dental check is carried out by patient's own dental practitioner before treatment starts.
16. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
17. Treatment should be agreed in the relevant MDT

Note: The greatest risk of thrombosis (CNS and central line related) is in early induction. The presence of a central catheter considerably increases this risk and there is some evidence that survival is affected. Consider delaying indwelling central venous catheterization until the end of phase I induction.

DRUG REGIMEN / CYCLE FREQUENCY

STEROID PRE-PHASE

All patients should be treated with a pre-phase of Dexamethasone 6mg/m^2/day, PO for 5 to 7 days.

PHASE 1 INDUCTION: WEEKS 1 to 4

Days 1, 8, 15 & 22	**DAUNORUBICIN** 30mg/m^2 in 100ml 0.9% Sodium Chloride IVI over 20 minutes into the side arm of a freely running 0.9% Sodium Chloride infusion **VINCRISTINE** 1.4mg/m^2 (max 2mg) in 50ml 0.9% Sodium Chloride IVI over 10 minutes
Days 1 to 4 **Days 8 to 11** **Days 15 to 18**	**DEXAMETHASONE** 10mg/m^2 (max 20mg) PO once daily with breakfast
Day 4	**PEGYLATED ASPARAGINASE (ONCASPAR®)** 1000IU/m^2 in 100ml 0.9% Sodium Chloride over 1 to 2 hours into a free flowing infusion **** <u>ONLY</u> for Philadelphia <u>Negative</u> patients aged <u>≤ 40yrs</u> **** **Omit Day 4** Pegylated Asparaginase for Ph -ve patients **<u>aged ≥41;</u>** these patients should only receive Day 18 Pegylated Asparaginase.
Day 14	**METHOTREXATE** 12.5mg INTRATHECAL*
Day 18	**PEGYLATED ASPARAGINASE (ONCASPAR®)** 1000IU/m^2 in 100ml 0.9% Sodium Chloride over 1 to 2 hours into a free flowing infusion **** <u>ONLY</u> for Philadelphia <u>Negative</u> patients ****
Days 1 to 28 (Continuous)	**IMATINIB** 400mg PO once daily. Dose escalate to 600mg PO once daily within 2 weeks, if tolerated. Continue until transplant wherever possible. **** <u>ONLY</u> for Philadelphia <u>Positive</u> patients ****

* 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.*

RESTAGING

Following Phase 1 recovery (ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L), remission should be confirmed by morphological bone marrow examination. The bone marrow aspirate must be 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.

DOSE MODIFICATIONS

Haematological toxicity:

Do NOT dose reduce on basis of blood count.

Renal/Hepatic impairment:

DAUNORUBICIN- Discuss with consultant

Renal impairment	Hepatic impairment
Cr < 105micromol/L 100% dose Cr 105-265micromol/L 75% dose Cr > 265micromol/L 50% dose	**Hyperbilirubinemia** Bilirubin < 50 micromol/L : 100% dose Bilirubin ≥ 50 micromol/L but < 90 : 50% dose Bilirubin ≥ 90 micromol/L but < 120 : 25% dose Bilirubin ≥ 120 micromol/L : omit dose Do not alter dose for abnormal transaminases.
Cardiac Toxicity: Daunorubicin Maximum cumulative dose (additive to other anthracyclines) 600 mg/m2 (in normal cardiac function) 400 mg/m2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation).	

VINCRISTINE- Discuss with consultant

Renal impairment	Hepatic impairment
No dose reduction necessary	**Hyperbilirubinemia** Bilirubin > 50 micromol/L: withhold. Bilirubin 25–50 micromol/L : Administer 50% of dose Do not alter dose for abnormal transaminases.
Neurotoxicity: In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding Vincristine with a consultant.	

IMATINIB- Discuss with consultant

Any severe non-haematological toxicity- Withhold treatment until resolved.
Resume treatment depending on the initial severity of the event.

Renal impairment	Hepatic impairment
Use with caution. 400mg minimum dose. Reduce if not tolerated. Increase dose for lack of efficacy.	400mg minimum dose with any impairment. 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

PEGYLATED-ASPARAGINASE (ONCASPAR®)- Discuss with consultant

Renal impairment	Hepatic impairment
No dose adjustment necessary	Because of the risk of severe liver toxicity, liver function tests should be performed regularly. Withhold if total bilirubin > 50. Do not alter dose for abnormal transaminases.

INVESTIGATIONS

- FBC, Coagulation screen.
- Creatinine, U&Es, LFTs
- Amylase, LFTs, glucose, clotting screen and fibrinogen should be monitored regularly during L-asparginase treatment.

CONCURRENT MEDICATION

Tumour lysis prophylaxis Risk stratify as per local policy	**Allopurinol** 300mg PO once daily. Start 24 hours prior to chemotherapy and continue for 5 days minimum; **OR** **Rasburicase** if WCC > 100 x 10^9/L or patient has bulky disease e.g. Large mediastinal mass or elevated urate at diagnosis. As per local policy
Aciclovir	200mg three times a day continuous
PJP prophylaxis	**Co-trimoxazole** 960mg PO twice a day for 2 days each week; If allergic or unable to tolerate co-trimoxazole, then monthly **pentamidine** 4mg/kg (max 300mg) in 100ml 0.9% Sodium Chloride IVI over 60 minutes

AMBISOME®	7mg/kg in 500ml 5% Glucose IVI over 2 hours **once weekly. Monitor renal function closely and consider omission of AmBisome in the event of renal impairment.** **Aim to give first dose on between Day 4-7.** *****Do not give azoles as antifungal prophylaxis within 72 hours before or after vincristine***.**
Proton pump inhibitor	As per local formulary
Norethisterone	5-10mg PO TDS until platelets >100x 10^9/L with recovery (menstruating women only)

ANTI-EMETICS

Days 1, (4), 8, 15, (18), 22	Low-Moderate Emesis risk
All other days	Low Emesis risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Note: Patients must be consented for induction phase 1 and 2 as a single programme of treatment i.e. “ALL Induction.”

Main side effects experienced during Induction 1 include: Nausea/vomiting, myelosuppression, infections, liver toxicity and hair loss, nerve damage (including confusion, constipation, pins-and-needles in hands and feet, weakness leading to difficulty in flexing ankle). The neurological problems are usually related to vincristine. Steroid related side effects.

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.

Peg-asparagase (ONCASPAR®): L-asparagase is associated with numerous toxicities including hepatic dysfunction, coagulopathy and thrombo-haemorrhagic complications, pancreatitis, hyperglycaemia and hyperlipidaemia. Thromboprophylaxis is recommended in patients with Plt > 50 x 10^9/L.
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 ®.

Erwinia L-asparaginase (ERWINASE ®):

In the case of hypersensitivity to pegylated asparagase, each dose of peg-asparagase (Oncaspar®) should be replaced with 6 doses of 20,000 units/m^2 Erwinase® intramuscular injection given on Mondays, Wednesdays and Fridays.

(Note: If the administered volume is over 4ml the individual dose may be split between two injection sites)

Further detailed information on managing specific adverse events can be found on UKALL14 trial protocol.

MORTALITY

Overall mortality for induction 1 and 2 is 5%.

REFERENCES

1. UKALL14. A randomized trial for adults with newly diagnosed acute lymphoblastic leukaemia. Eudract No: 2009-012717-22. Version 12.0, 26.06.2018.
2. The North London Cancer Network Dosage Adjustment for Cytotoxics in Renal Impairment. UCLH Version 3 updated January 2009.
3. The North London Cancer Network Dosage Adjustment for Cytotoxics in Hepatic Impairment. UCLH Version 3 updated January 2009.
4. Imatinib (Glivec). Summary of product characteristics. Last Updated on eMC Updated 20-May-2019.
5. Pegaspargase (Oncaspar®). Summary of product characteristics. Last Updated on eMC 09-May-2019.
6. Erwinia L-asparaginase ERWINASE ®. Summary of product characteristics. Last Updated on eMC 23-Feb-2017

Review

Name	Revision	Date	Version	Review date
Julia Wong Nadjoua Maouche Dr Andy Peniket	New protocol	April 2017	1.0	April 2019
Cheuk-kie Cheung	General formatting	May 2017	1.1	April 2019
Jon Barrett Haematology Pharmacist. NSSG Myeloid Group	Annual Protocol meeting	October 2019	1.2	October 2021