ALL PHASE 1 INDUCTION (25 - 60 years)

INDICATION

Induction treatment in adult acute lymphoblastic leukaemia (ALL).

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

Curative

PRE-ASSESSMENT

1. Blood tests - FBC, reticulocyte count, & film with an additional sample for flow cytometry for cell markers in case of high WCC and no marrow available. Group & Screen. PT, APTT, fibrinogen, D dimers. Creatinine, electrolytes & LFT's, LDH, CRP, calcium, phosphate, magnesium, urate, CRP, Thyroid function tests. Random glucose. B12, folate, iron profile. CMV IgG and IgM, EBV IgG, Hepatitis B core Ab + sAg, Hepatitis C Ab screen, HSV & HZV serology, HIV Ag/Ab screen.
2. Bone marrow aspirate and trephine
3. Confirm disease diagnosis from bone marrow aspirate (or peripheral blood where there is circulating disease) 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 there is any suspicion of neurological disease: MRI head/spine, perform lumbar 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 each treatment cycle in women with childbearing potential, unless they have been sterilised or undergone a hysterectomy
9. ECG +/- Echo
10. Record performance status (WHO/ECOG)
11. Record height and weight.
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.
    - Patients must be consented for induction phase 1 and 2 as a single programme of treatment i.e. "ALL Induction."
13. Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice.
14. Assess tumour lysis syndrome (TLS) risk in line with TLS protocol, request appropriate hydration and prophylactic treatment as indicated.
15. Consider dental assessment / advise dental check is carried out by patient's own dental practitioner before treatment starts.
16. Treatment should be agreed in the relevant MDT

17. QRISK3 score (some TKIs have been associated with increased risk of cardiovascular disease and vascular risk factors should be considered and managed as appropriate)
18. TPMT (thiopurine methyltransferase) and NUDT15 genotyping to identify inherited variants that predict low enzyme activity and high risk of toxicity from 6-mercaptopurine. Request screening early to allow results to be available prior to mercaptopurine use in future ALL treatment.
19. Philadelphia negative patients - 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 receive a pre-phase treatment:

	DEXAMETHASONE 6 mg/m^2 PO OD in the morning, with food for 5 - 7 days.

PHASE 1 INDUCTION (4 weeks)

Consider addition of **rituximab** in B-ALL **CD20 positive** patients.

Scheduled dosing	Treatment details
Days 1, 8, 15, 22	**DAUNORUBICIN** 30 mg/m^2 via IV infusion in 100ml 0.9% sodium chloride over 20 minutes **VINCRISTINE** 1.4 mg/m^2 (max 2mg) via IV infusion in 50ml 0.9% sodium chloride over 10 minutes
Days 1 - 4, 8 - 11, 15 - 18, 22 - 25	**DEXAMETHASONE** 10mg/m^2 (max 20mg) PO once daily in the morning with food
Day 14*	**METHOTREXATE** 12.5mg INTRATHECAL

* Timing of intrathecal therapy can be adjusted to accommodate logistical issues.

➢ **If Philadelphia POSITIVE (Ph +ve) disease:**

Continuous treatment	**IMATINIB** 600mg PO once daily (or maximum tolerated dose) Continue throughout all treatment, including breaks between regimens up until transplant where possible. Imatinib 90-day Aria support is available.

➢ **If Philadelphia NEGATIVE (Ph -ve) disease:**

Day 4 and 18 **OMIT day 4 if age ≥ 41 yrs**	**Pre-medication (30 mins prior to dose):** • Paracetamol 1g PO once only • Famotidine PO 20mg once only **PEGYLATED ASPARAGINASE (ONCASPAR®)** 1000 IU/m^2 via IV infusion in 100ml sodium chloride 0.9% over 1 to 2 hours

Hypersensitivity - Each dose of peg-asparaginase (Oncaspar®) can be replaced with 3 doses of 20,000 units/m^2 crisantaspase / L-asparaginase (Erwinase®) intramuscular injection given on Mondays, Wednesdays and Fridays.

TRAUMATIC LUMBAR PUNCTURE

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 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 impairment

Daunorubicin	**GFR 30 - 49 ml/min**: 75% dose **GFR < 30 ml/min**: 50% dose
Imatinib	No adjustment should be required; however, the manufacturer recommends caution.
Mercaptopurine (6-MP)	**GFR < 30 ml/min:** Consider increasing dosing interval to every 48 hours
Peg-asparaginase (Oncaspar®) or crisantaspase / L-asparaginase	No dose adjustment necessary - degraded by proteolytic degradation. No renal clearance.
Vincristine	No dose reduction necessary

Hepatic impairment

ULN = Upper limit of normal.

Daunorubicin	**Bilirubin > ULN to 2 x ULN:** 75% dose **Bilirubin > 2 x ULN:** 50% dose Do not alter dose for abnormal transaminases.
Imatinib	Imatinib is mainly metabolised through the liver. Use with caution, consider dose reduction if signs of intolerance. **Bilirubin > 3 x ULN (not Gilberts related) or liver transaminases > 5 x ULN:** Withhold treatment until bilirubin < 1.5 x ULN and LFTs < 2.5 x ULN. On improvement, resume at reduced dose e.g. Reduce from 400mg to 300mg; or 600mg to 400mg.
Mercaptopurine (6-MP)	**On treatment start:** • **Mild impairment:** No dose adjustment necessary • **Moderate impairment:** Consider starting treatment with a lower dose or increase the dosing interval. • **Severe impairment:** Not recommended Mercaptopurine is associated with a high rate of serum aminotransferase elevations which can be accompanied by jaundice. **Bilirubin > 2 x ULN:** Withhold mercaptopurine until bilirubin improves to baseline. Then restart at half the previous dose. Escalate from 50% to 75% to 100% dose at 7 or 10-day intervals provided that hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotransferases although if ALT/AST >10 x ULN discuss with consultant.
Peg-asparaginase (Oncaspar®) or crisantaspase / L-asparaginase	Because of the risk of severe liver toxicity, liver function tests should be performed regularly. **Bilirubin > 3 x ULN or transaminases > 10 x ULN:** Withhold treatment.
Vincristine	**Bilirubin > 50 micromol/L:** Reduce to 50% dose

Other toxicities

Anthracycline cumulative dosing
Assess for previous anthracycline use and calculate existing exposure and intended exposure.

Maximum cumulative dose of non-liposomal daunorubicin:

- 600 mg/m2 (in normal cardiac function)
- 400 mg/m2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation).

Neurotoxicity
In the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with a consultant.

Pancreatitis
If suspected pancreatitis, suspend any asparaginase treatment, if confirmed then permanently discontinue treatment.

INVESTIGATIONS

- FBC,
- U&Es, LFTs
- At clincian's discretion: Amylase, glucose, coagulation screen and fibrinogen during peg-asparginase or L-asparginase treatment.

CONCURRENT MEDICATION

TLS prophylaxis	Allopurinol PO 300mg OD for 7 days, or rasburicase in higher risk patients in line with TLS protocol, combine with PO/IV hydration.
Viral prophylaxis	Aciclovir 200 mg PO TDS continuously throughout treatment, and during breaks before next treatment phase.
PJP prophylaxis	Co-trimoxazole 960 mg PO BD on Saturday and Sunday. In co-trimoxazole allergy/intolerance: Refer to alternate PCP prophylaxis options.
Fungal prophylaxis	High risk of fungal infection. **Avoid use of azoles due to weekly vincristine administration.** Use amphotericin B liposomal (formally known as AmBisome®) 7 mg/kg IV ONCE weekly - modified doses are recommended where there are renal concerns, see antifungal guidelines.
Gastroprotection	Proton pump inhibitor (PPI, e.g. omeprazole) or H_2 receptor antagonist (H2RA, e.g. famotidine) in line with local formulary. Continue throughout treatment and for periods of persistent thrombocytopenia, or if other clinical reason to continue.
Menstrual suppression	Consider in all patients who have experienced menstruation in the past 6 months. Norethisterone 5 – 10 mg PO TDS. Increase dose to 10 mg if evidence of breakthrough bleeding. **OR** Medroxyprogesterone 10 mg PO TDS (if norethisterone unavailable)
Hepatitis B prophylaxis	If hepatitis B surface antigen (HBsAg) or hepatitis B core antibody positive - prophylaxis or additional monitoring may be indicated, please see Pathway for treatment of Hepatitis B in the setting of immunosuppressive therapy guidance.

EMETIC RISK

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

EXTRAVASATION RISK

Daunorubicin: Vesicant
Vincristine: Vesicant

Peg-asparginase / L-asarginase: Neutral
Rituximab: Neutral

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This section includes highlighted adverse event / side-effect information and does not intend to be a fully inclusive list of every possible reported event. For full information please reference the individual drug SmPCs on www.medicines.org.uk.

Common side-effects (Induction, phase 1): 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.

Daunorubicin: Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), cardiotoxicity, alopecia, red discolouration of urine, infection, deranged LFTs

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-asparaginase (Oncaspar®) or crisantaspase / L-asparaginase (Erwinase®): Hepatic dysfunction, coagulopathy and thrombo-haemorrhagic complications, pancreatitis, hyperglycaemia and hyperlipidaemia. Hypersensitivity including anaphylactic reactions can occur during/after administration. VOD/SOS.

Rituximab: Infusion reactions, cytokine release syndrome, hepatitis B reactivation

Vincristine: Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), neurotoxicity, constipation, peripheral neuropathy, deranged LFTs

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DRUG INTERACTIONS

Omission of a medication in the information below does not guarantee safety in combination with treatment as new therapies and evidence can emerge over time. Consult SmPC or alternate reference sources / pharmacist if further information is required.

Daunorubicin

- **Concurrent use of cardiotoxic drugs:** Concurrent use of other drugs with risk of cardiotoxicity requires caution and closer cardiac monitoring.
- **Concurrent use of hepatotoxic drugs:** Daunorubicin is primarily metabolised in the liver, use of hepatotoxic drugs may affect the metabolism or pharmacokinetics of daunorubicin. This can potentiate any adverse effects. Avoid concurrent use where possible, refer to dose modifications section for advice on management of deranged LFTs.

Imatinib

- **CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.):** Increased toxicity of imatinib possible due to reduced clearance, monitor and adjust imatinib dose if required.
- **CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.):** Reduced efficacy of imatinib possible due to increased clearance, if unable to avoid combination titrate to maximum tolerated dose and be aware of possible reduced clinical efficacy.

- **CYP3A4 metabolised drugs (e.g. benzodiazepines, dihydropyridine calcium channel blockers, calcineurin inhibitors, statins):** Imatinib is a moderate inhibitor of CYP3A4 and may increase concentrations of drugs metabolised via CYP3A4, particularly if involving a narrow therapeutic index. The clinical relevance of this is interaction is unknown. Caution and monitoring for toxicity is recommended.

Peg-asparaginase (Oncaspar®) or crisantaspase / L-asparaginase (Erwinase®):

- **Concomittant oral anticoagulants or antiplatelets:** Concomitant use should proceed with caution due to changes in coagulation. Increased monitoring may be required in some cases.
- **Vincristine:** Immediately preceding or concomitant treatment with vincristine can increase the toxicity of pegaspargase and increases the risk of anaphylactic reactions. Administer vincristine 12 hours prior to pegaspargase to minimise toxicity.

Rituximab:

- **Anti-hypertensives:** Consider withholding antihypertensive medications 12 hours prior to the rituximab infusion to avoid exacerbating hypotensive effects.

Vincristine:

- **CYP3A4 and P-gp inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, macrolides, ciclosporin, grapefruit juice etc.):** Increased toxicity of vincristine possible due to reduced clearance, monitor for vincristine toxicity (particularly neurotoxicity, paralytic ileus).
- **CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.):** Reduced efficacy of vincristine possible due to increased clearance.
- **Ototoxic drugs (e.g. cisplatin, aminoglycosides, frusemide, NSAIDs):** Additive ototoxicity. Avoid combination or perform regular audiometric testing.

VACCINATIONS

All patients should be advised to avoid live vaccination throughout treatment. Administration of non-live vaccination is possible but response and resultant immunity may be compromised due to impaired immune response. See below for timing considerations.

Seasonal vaccination (e.g. flu or COVID vaccinations) may be given but responses during treatment will be sub-optimal.

Other non-live vaccinations should be given at least 2 weeks prior to treatment or deferred to at least 2 weeks post-chemotherapy. Patient's neutrophils should ideally be > 0.75 x 10^9/L. Studies that have evaluated antibody response to vaccines during chemotherapy have mostly done so during the maintenance phase of ALL therapy.

MORTALITY

Overall mortality for induction 1 and 2 is 5%.

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Julia Wong Nadjoua Maouche Dr Andy Peniket	New protocol	Apr 2017	1.0	Apr 2019
Cheuk-kie Cheung	General formatting	May 2017	1.1	Apr 2019
Jon Barrett Haematology Pharmacist. NSSG Myeloid Group	Annual Protocol meeting	Oct 2019	1.2	Oct 2021
Yen Lim, Zishaan Ramzan Haematology Pharmacists, Connor Sweeney, Consultant Haematologist NSSG Myeloid Group	Annual Protocol meeting 2022	Aug 2023	2.0	Nov 2025
Donna Constantine Advanced Cancer Pharmacist NSSG Myeloid Group	Review of prior unpublished amendments. Rituximab addition for B-ALL. Additional toxicities added. Revision of supportive care recommendations. Pre-meds recommended for Peg-asp. Rationalisation of dose adjustment in line with SPC/trial/practical recommendations.	Aug 2025	3.0	Sept 2026