ALL PHASE 2 INDUCTION (25 - 60 years)

Intrathecal treatment MUST be administered in line with national guidance and local intrathecal policy

INDICATION

Continuation of induction treatment, following phase 1 treatment, 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

Curative

PRE-ASSESSMENT

Ensure all previous pre-assessments as per induction 1 have been completed, also:

1. Blood tests - FBC, U&Es, creatinine, LFTs.
2. Record performance status (WHO/ECOG).
3. Record height and weight.
4. Urine pregnancy test – before each treatment cycle in women with childbearing potential, unless they have been sterilised or undergone a hysterectomy
5. Consent – confirm patient was consented for induction phase 1 and 2 as a single programme of treatment i.e. “ALL Induction”. If missing, 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 and obtain written consent for phase 2.
6. Assess remaining tumour lysis syndrome (TLS) risk following Phase 1 treatment in line with TLS protocol, request hydration and prophylactic treatment if still indicated.
7. For patients prescribed oral systemic anti-cancer therapy (SACT), ensure pre-treatment counselling in line with recommendations for oral SACT.
8. Treatment should be agreed in the relevant MDT.
9. TPMT (thiopurine methyltransferase) and NUDT15 genotyping to identify inherited variants that predict low enzyme activity and high risk of toxicity from mercaptopurine, screening must be conducted early in treatment prior to receipt of mercaptopurine. In the presence of genetic variants, consult guidance on dose adjustments and monitoring.
10. Calculate QRISK3 score for risk of cardiovascular disease, due to risk with tyrosine kinase inhibitors (TKIs). Vascular risk factors should be managed as appropriate.

DRUG REGIMEN / CYCLE FREQUENCY

CYCLE 1 (4-week duration)

Treatment should begin following completion of phase 1 induction and on haematological recovery. Proceed when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L.

Scheduled dosing	Treatment details
Days 1 and 15	**CYCLOPHOSPHAMIDE** 1000 mg/m^2 in 250ml 0.9% sodium chloride over 30 minutes.
Days 1 - 4, 8 - 11 15 - 18, 22 – 25*	**CYTARABINE** 75 mg/m^2 slow IV bolus
Days 2, 9 16, 23**	**METHOTREXATE** 12.5 mg INTRATHECAL
Days 1 to 28	**MERCAPTOPURINE** 60 mg/m^2 PO once daily at the same time each day, at least 1 hour before or 3 hours after food or milk

* Timing of cytarabine can be adjusted to allow administration during the week providing the full dose is administered.

** 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.

RESTAGING

Following phase 2 recovery (ANC >0.75 x 10^9/l and Plt >75 x 10^9/l), remission should be confirmed by morphological bone marrow examination.

MRD assessment at the end of phase 2 is an important risk-stratifying factor, so due consideration must be given to making an extremely timely evaluation as soon as bone marrow has recovered.

However, progression to intensification or bone marrow transplant should be as swift as possible. If the patient is not in CR at the end of phase 2, protocol therapy ceases.

DOSE MODIFICATIONS

Haematological toxicity

Cycle 2 induction starts when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L.

Do NOT dose reduce on basis of blood count.

Renal impairment

Cyclophosphamide	**GFR 10 – 29 ml/min:** 75% dose **GFR < 10 ml/min:** Not recommended, but if unavoidable 50% dose
Cytarabine	No dose reduction necessary normally as not considered high 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

Hepatic impairment

ULN = Upper limit of normal.

Cyclophosphamide	**Mild and moderate:** No need for dose adjustment. **Severe:** Not recommended, due to risk of reduced efficacy
Cytarabine	**Mild / moderate impairment:** No dose adjustment necessary **Severe impairment:** 25 - 50% dose; increase as tolerated
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.

Other toxicities

Haemorrhagic cystitis
If gross haematuria develops, cyclophosphamide should be withheld until resolution of cystitis and mesna treatment commenced as per SmPC – discuss with consultant

INVESTIGATIONS

- FBC, U&Es, LFTs

CONCURRENT MEDICATION

Viral prophylaxis	Aciclovir 200 mg PO TDS continuously throughout treatment.
PJP prophylaxis	Co-trimoxazole 960 mg PO BD on Saturday and Sunday. In co-trimoxazole allergy/intolerance: Refer to alternate PCP prophylaxis on guidelines.
Fungal prophylaxis	High risk of fungal infection. Use of posaconazole or voriconazole is recommended in line with antifungal guidelines. Amphotericin B liposomal (formally known as AmBisome®) 7 mg/kg IV ONCE weekly is also an option - 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)
Bladder protection	Consider for patients with pre-existing bladder disorders or previous bladder toxicity to cyclophosphamide. Mesna IV 200 mg/m2 (20% of IV cyclophosphamide dose), immediately before cyclophosphamide injection, followed by mesna PO 400 mg/m2 (40% of IV cyclophosphamide dose) at 2 and 6 hours after the IV mesna dose. In patients at high risk of urothelial toxicity, a shorter interval may be left between mesna doses, the number of doses increased, or both.
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

Day 1 and 15: Moderate - High

Other days: Low - Moderate

EXTRAVASATION RISK

Cyclophosphamide: Neutral
Cytarabine: 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 2): Nausea and vomiting, myelosuppression, infections, liver toxicity, renal toxicity (usually via liposomal amphotericin use) and hair loss.

Cytarabine: Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), nausea, diarrhoea, abdominal pain, oral ulceration, hepatic dysfunction, CNS, GI and pulmonary toxicity, reversible corneal toxicity (usually related to intensive dosing), somnolence, convulsion, pulmonary oedema.

"Cytarabine syndrome" can occur, characterised by flu-like symptoms, skin rash and occasionally chest pain –presenting 6 to 12 hours after cytarabine administration. Symptoms generally resolve within 24 hours of completing therapy.

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.

Mercaptopurine: Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), anorexia, nausea and/or vomiting, pancreatitis, stomatitis, biliary stasis, hepatotoxicity

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

---

DRUG INTERACTIONS

Cyclophosphamide

- **Strong CYP3A4 inducers (e.g. carbamazepine, rifampicin, phenytoin, St John's Wort etc.):** Increased toxicity of cyclophosphamide possible due to increased conversation to active and inactive metabolites. Avoid concurrent use or monitor closely for toxicity.
- **Strong CYP3A4 inhibitors (e.g. grapefruit juice, clarithromycin, triazole antifungals etc.):** Theorised major interaction. May reduce cyclophosphamide efficacy due to decreased conversion to active and inactive metabolites**.** Avoid concurrent use.
- **Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, furosemide, NSAIDs):** Risk of additive nephrotoxicity, only use if benefit outweighs risk.
- **Amiodarone:** Increased risk of pulmonary toxicity in combination treatment. Consider benefit vs. risk, consider alternate treatment.

- **Allopurinol, hydrochlorothiazide, indapamide:** Increased risk of bone marrow depression; probably due to reduced clearance of active metabolites of cyclophosphamide, avoid where possible.
- **Drugs with hyponatraemic effects:** Concurrent use of other drugs with risk of SIADH (e.g. SSRIs, diuretics, carbamazepine etc.) may increase cumulative risk of SIADH during transplant.

Cytarabine

- **Cytidine deaminase (CDA) inhibitors (e.g. cedazuridine) -** Potential increased toxicity of cytarabine due to reduced clearance. There are no NHS-approved treatments of this type in the UK currently.
- **Intrathecal methotrexate:** Possible increased risk of severe neurological adverse reactions such as headache, paralysis, coma and stroke like episodes.

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.

Mercaptopurine

- **Allopurinol / trimethoprim / febuxostat:** Increases the risk of haematological toxicity when given with mercaptopurine. Avoid if possible, otherwise mercaptopurine dose adjustment may be required.

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

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. Novartis. Imatinib (Glivec) 400mg film-coated tablets. Summary of Product Characteristics. Updated 24/5/2022. Accessed 23/08/2023 via https://www.medicines.org.uk/emc
3. Giraud, E.L. et al. (2023) 'Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: An update', The Lancet Oncology, 24(6). doi:10.1016/s1470-2045(23)00216-4
4. London Integrated Care Systems (ICSs) Guidelines for Safe Prescribing, Handling and Administration of Systemic AntiCancer Therapy. Accessed 23/8/2023 via: https://rmpartners.nhs.uk/wp-content/uploads/2017/03/pan-london-cytotoxic-handbook-july-2015.pdf
5. Yallop, D, Chauhan, D and Palmer, R. Guideline for 6-mercaptopurine dosing in adult acute lymphoblastic leukaemia based on *TPMT* and *NUDT15* genotypes. Version 1.0. British Oncology Pharmacy Association. 15/03/2023

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. Addition of imatinib.	Aug 2023	2.0	Nov 2025
Donna Constantine, Advanced Cancer Pharmacist NSSG Myeloid Group	Review of prior unpublished amendments. Addition of rituximab for B-ALL patients. New interactions & vaccination section. General formatting and minor text adjustments. Updates to supportive care recommendations.	Jun 2025	3.0	Sep 2026