ALL Phase 2 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:

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

1. Blood tests - FBC, creatinine, LFTs
2. Record performance status (WHO/ECOG)
3. Record height and weight (also needed to calculate CrCl)
4. 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
5. 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
6. 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
7. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
8. Treatment should be agreed in the relevant MDT

DRUG REGIMEN / CYCLE FREQUENCY

To commence following haematopoietic recovery from induction phase 1 i.e. when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L

PHASE 2 INDUCTION: WEEKS 5 to 8

Days 1 & 15	**CYCLOPHOSPHAMIDE** 1000mg/m^2 in 250ml 0.9% Sodium Chloride IVI over 30 minutes.
Days 2 to 5 **Days 9 to 12** **Days 16 to 19** **Days 23 to 26**	**CYTARABINE** 75mg/m^2 slow IV bolus (concentration 20mg/ml)
Days 1, 8, 15 & 22	**METHOTREXATE** 12.5mg INTRATHECAL
Days 1 to 28	**MERCAPTOPURINE** 60mg/m^2 PO once daily at the same time each day, at least 1 hour before or 3 hours after food or milk
Days 1 to 28 (continuous)	**IMATINIB** 600mg PO once daily with a meal and a large glass of water. Continue until transplant wherever possible. **** <u>ONLY</u> for Philadelphia <u>Positive</u> patients ****

Note: Timing of Intrathecal therapy can be moved +/- 3 days to allow administration on specified lists as per local and national guidance. Likewise, timing of the cytarabine blocks can be scheduled so that they can take place during the week as long as the full doses are given.

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. In patient with no high risk factors at diagnosis**,**

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/hepatic impairment:

CYCLOPHOPHAMIDE- Discuss with consultant

Renal impairment	Hepatic impairment
Clinical decision – consider whether patient is being treated with high dose treatment. CrCl > 20ml/min 100% dose CrCl 10-20ml/min 75% dose CrCl < 10ml/min 50% dose	Clinical decision. Exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary.

CYTARABINE- Discuss with consultant

Renal impairment	Hepatic impairment
No dose reduction necessary	**Hyperbilirubinaemia** Bilirubin < 50 full dose Bilirubin ≥ 50 but < 90 : 50% dose Bilirubin ≥ 90 but < 120 : 25% dose Bilirubin ≥ 120 omit dose Do not alter dose for abnormal transaminases.

MERCAPTOPURINE- Discuss with consultant

Renal impairment	Hepatic impairment
Caution / clinical decision. Consider increasing dosing interval to every 48hrs if CrCl 10-50ml/min	**Hyperbilirubinaemia:** Bilirubin >50micromol/L - omit mercaptopurine until it is less than 20micromol/L and then restart at half the previously dose. Escalate from 50% to 75% to 100% dose at 10-day intervals provided that hyperbilirubin-aemia does not recur. Do not modify dosage for elevated aminotransferases.

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

INVESTIGATIONS

- FBC, Coagulation screen.
- Creatinine, U&Es, LFTs

CONCURRENT MEDICATION

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
Fungal prophylaxis	As per local protocol (Azoles may be used in Phase 2 Induction)
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

Day 1 and 15	Moderate – High Emesis risk
Days 1 to 14, 16 to 28	Low to Low-Moderate 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 2 include: Nausea/vomiting, myelosuppression, infections, liver toxicity and hair loss,

Imatinib: Neutropenia, thrombocytopenia, anaemia, hepatotoxicity, headache, nausea, diarrhea, vomiting, dyspepsia, abdominal pain, fluid retention, dermatitis, muscle spasm and cramps, musculoskeletal pain. Reactivation of HBV has also been reported.

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.

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