ALL CONSOLIDATION- Cycle 1 (25-60 years)

INDICATION

Adult Acute Lymphoblastic Leukaemia (ALL) in remission not eligible for allogeneic transplantation

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.

Patients with CNS involvement: cranial irradiation will be given before consolidation begins. Mercaptopurine maintenance should be given throughout the period of CNS irradiation. In the event of cytopenias, Mercaptopurine should be reduced or omitted rather than delaying radiotherapy. Mercaptopurine should be continued at max 75mg/m^2 in the absence of cytopenias.

TREATMENT INTENT

Curative or to maximize remission.

PRE-ASSESSMENT:

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

1. Blood tests - FBC, creatinine, LFTs
2. 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
3. Record performance status (WHO/ECOG)
4. Record height and weight (also needed to calculate CrCl)
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. Patients must be consented for consolidation cycles 1-4 as a single programme of treatment i.e. “ALL consolidation.” Obtain written consent on the day of treatment.
6. Treatment should be agreed in the relevant MDT

DRUG REGIMEN / CYCLE 1

Cycle 1 should begin after Intensification, when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L.

Days 1 to 5	**CYTARABINE** 75mg/m^2 slow IV bolus (concentration 20mg/ml)
Days 1 to 5	**ETOPOSIDE** 100mg/m^2 in 500ml 0.9% Sodium Chloride (final concentration 0.2 to 0.4mg/ml) IVI over 60 minutes
Day 1	**METHOTREXATE** 12.5mg INTRATHECAL
Day 5	**PEGYLATED ASPARAGINASE (ONCASPAR®)** 1000IU/m^2 in 100ml 0.9% Sodium Chloride IVI over 1 to 2 hours into a free flowing infusion **** ONLY for Philadelphia Negative patients ****
Continuous	**IMATINIB** 600mg PO once daily **** ONLY for Philadelphia Positive patients ****

Timing of Intrathecal therapy can be moved +/- 3 days to allow administration as per local 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.

DOSE MODIFICATIONS

Haematological toxicity:
Cycle 1 consolidation starts after Intensification, when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L.
Do NOT dose reduce on basis of blood count.

Hepatic/Renal Impairment:

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.

ETOPOSIDE- Discuss with consultant

Renal impairment	Hepatic impairment
GFR (ml/min) Dose > 50 100% 15-50 75% < 15 50% Subsequent doses should be based on clinical response. **Dialysis** Start at reduced dose and increase according to clinical response.	Arguments for and against dose reduction. Bilirubin 26-51micromol/L or AST 60-180u/L -50% dose Bilirubin >51micromol/L or AST >180u/L -clinical decision

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 with pegylated-asparaginase, liver function tests should be performed regularly while patients are being treated with this drug. 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

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
FLUCONAZOLE	50mg PO once daily continuous
Proton pump inhibitor	As per local formulary
Norethisterone	5-10mg PO TDS until platelets >100x 10^9/L with recovery (menstruating women only)

ANTIEMETICS

Days 1 to 5 Low-Moderate emesis risk
Day 6-onwards Low emesis risk

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

Note: Patients must be consented for consolidation cycles 1-4 as a single programme of treatment i.e. “ALL consolidation.”

Main side effects experienced during consolidation include: nausea and 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 which appears in Consolidation 3. **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®): L-asparaginase is associated with numerous toxicities including hepatic dysfunction, coagulopathy and thrombo-haemorrhagic complications, pancreatitis, hyperglycaemia and hyperlipidaemia. Thromboprophylaxis is recommended in patients 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 asparginase, each dose of peg-asparginase (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

Treatment related risk for overall ALL consolidation for patients in remission is approximately 1%

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.
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3. The North London Cancer Network Dosage Adjustment for Cytotoxics in Hepatic Impairment. UCLH Version 3 updated January 2009.
4. London Cancer Alliance North and South. Haemato-Oncology Clinical Guidelines, Acute Leukaemias and Myeloid Neoplasms Part 1: Acute Lymphoblastic Leukaemia. April 2015.
5. Imatinib (Glivec). Summary of product characteristics. Last Updated on eMC Updated 20-May-2019.
6. Pegaspargase (Oncaspar®). Summary of product characteristics. Last Updated on eMC 09-May-2019.
7. 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