ALL CONSOLIDATION- Cycle 3 (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.

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 3

This phase runs from Day 1 to 42 inclusive (i.e. for 6 weeks in total). Patients should have ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L to start and have recovered again to this level before Day 29 starts. Once begun, therapy is not interrupted for myelosuppression alone. Any serious infection, such as Varicella, pneumocystis pneumonia, neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during this phase.

To commence 3 weeks from Cycle 2 Day 1 or when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L.

DAYS 1 to 28

Days 1, 8, 15, 22	**DAUNORUBICIN** 25mg/m^2 in 100ml 0.9% Sodium Chloride IV 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 IV over 10 minutes.
Days 1 to 4 **Days 8 to 11** **Days 15 to 18** **Days 22 to 25**	**DEXAMETHASONE** 10mg/m^2 (max 20mg) PO once daily in the morning
Days 2 and 17	**METHOTREXATE** 12.5mg INTRATHECAL.
Day 4	**PEGYLATED ASPARAGINASE (ONCASPAR®)** 1000 IU/m^2 in 100ml 0.9% Sodium Chloride IVI over 1 to 2 hours into a free flowing infusion **** ONLY for Philadelphia Negative patients ****
Days 1 to 28 **Continuous**	**IMATINIB** 600mg PO once daily. **** ONLY for Philadelphia Positive patients ****

DAYS 29 to 42 (To commence when ANC >0.75x10^9/L and platelets >75x10^9/L)

Day 29	**CYCLOPHOSPHAMIDE** 1000mg/m^2 IV bolus (concentration 20mg/ml)
Days 29 to 42	**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 30 to 33 **Days 37 to 40**	**CYTARABINE** 75mg/m^2 slow IV bolus (concentration 20mg/ml)
Days 29 to 42	**IMATINIB** 600mg PO once daily. **** ONLY for Philadelphia Positive patients ****

DOSE MODIFICATIONS

Haematological toxicity:

Cycle 3 Consolidation (Delayed intensification) - commence 3 weeks from Cycle 2 Day 1 or when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L. Patients should also have recovered to ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L before Day 29 starts.

Renal/Hepatic Impairment/other toxicity:

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.	

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.

Myeloid group

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

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.

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 hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotranseferases.

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 Check LFT's only if patient jaundiced. 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
Fungal prophylaxis	**As per local protocol** *****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, 8, 15, 22	Low-Moderate Emesis risk
Day 29	Moderate - High Emesis risk
All other days	Low to Low-Moderate 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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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