Thames Valley
Strategic Clinical Network

ALL MAINTENANCE (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. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see Fertility Guidelines)
6. 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 maintenance.” Obtain written consent on the day of treatment.
7. Treatment should be agreed in the relevant MDT
8. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures

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DRUG REGIMEN / CYCLE FREQUENCY

Start when ANC > 0.75 x 10^9/L and Plt > 75 x 10^9/L following Consolidation Cycle 4.

Cycles are repeated every 3 months for 2 years.

It is recommended that patients are reviewed at least every 4 weeks. Mercaptopurine and methotrexate should generally be prescribed every 4 weeks to enable dose variations (see below). If a dose increase is indicated, increase the dose of the next 4 week block to be prescribed to minimise dose alterations in cycle.

Day 1	**VINCRISTINE** 1.4mg/m^2 (max 2mg) in 50ml 0.9% Sodium Chloride IVI over 10 minutes
Days 1 to 5	**PREDNISOLONE** 60mg/m^2 PO once daily with breakfast
Weekly	**METHOTREXATE*** 20mg/m^2 (2.5mg tablets) PO once per week (not to be given on the same day as Co-trimoxazole)
Day 2	**METHOTREXATE** 12.5mg **INTRATHECAL** every 3 months (To be given once ANC = 0.75 x 10^9/L and Plt = 75 x 10^9/L)
Daily (continuous)	**MERCAPTOPURINE*** 75mg/m^2 PO once daily at the same time each day, at least 1 hour before or 3 hours after food or milk
Daily (continuous)	**IMATINIB** 600mg PO once daily. Continue throughout Maintenance. **** ONLY for Philadelphia Positive patients ****

***See section below for methotrexate and mercaptopurine dose modifications.**

DOSE MODIFICATIONS

Target Blood count range

Adjust dosing of maintenance therapy to maintain **ANC 0.75 - 1.5 x10^9/L and Plt 75 - 150 x10^9/L** Doses may need to be both increased and reduced from starting dose to maintain the correct level of haematological suppression.

ANC (x10^9/L)		Plt (x10^9/L)	Dose adjustment
> 1.5	AND	> 150	Increase Mercaptopurine dose by 25% If counts remain at these levels after 4 weeks, increase oral Methotrexate by 25%. There are no maximum doses of Mercaptopurine and oral Methotrexate.
< 0.75	OR	< 75	Reduce Mercaptopurine and oral Methotrexate by 50%
< 0.5	OR	< 50	Stop maintenance and restart at 100% when ANC >0.75 and Plt >75

Maintenance should not be interrupted unnecessarily, with the exception of Intrathecal Methotrexate. If doses are omitted for cytopenias or infectious complications, they do not need to be made up with additional doses later.

If cytopenias occur and maintenance is halted, consider stopping Co-trimoxazole if blood counts do

not recover within 2-3 weeks. Doses of Mercaptopurine and oral Methotrexate should not be compromised in order to permit continuation of Co-trimoxazole. Alternative prophylaxis against PJP should be given.

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.	

ORAL METHOTREXATE

Renal impairment	Hepatic impairment
If serum creatinine >3x baseline, omit MTX until completely resolved. Resume at 100% of the previously attained dose and continue at 10-day intervals.	If bilirubin > 50micromol/L omit until < 20micromol/L, then restart at half of previously attained 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 aminotransferases although if ALT/AST > 500 iu/l discuss with consultant.
Mucositis: For Grade 2 mucositis of > 3 days duration, decrease dose by 30%. For Grade 3 - 4 mucositis, withhold until resolved; resume at 50% of previously attained dose and subsequently escalate to 75% to 100% dose at 10 day intervals provided Grade 3 - 4 toxicity does not recur. Consider culturing lesions for herpes simplex if mucositis persists or recurs.	

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 hyperbilirubinaemia does not recur. Do not modify dosage for elevated aminotranseferases although if ALT/AST > 500 iu/l discuss with consultant..

IMATINIB

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, 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 **(AVOID on the same day as the weekly oral Methotrexate)** 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.
Proton pump inhibitor	As per local formulary for the duration of steroid treatment in regimen (discuss with consultant)
Note: Antifungal prophylaxis is not generally required during maintenance therapy unless the patient is deemed to be high risk for fungal disease.	

ANTI-EMETICS

Low-Moderate emesis risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Main side effects experienced during maintenance phase: Nausea, Low blood counts, infections, liver toxicity, mucositis, nerve damage (including confusion, constipation, pins-and-needles in hands and feet, weakness leading to difficulty in flexing ankle). Steroid side effects.

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

The treatment related mortality risk for patients in remission on maintenance is low (less than 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.
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. 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.

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