ALL INTENSIFICATION / CNS PROPHYLAXIS (25-60 years)

INDICATION

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.

Note: This regime may be omitted if a myeloablative transplant is to be carried out. If there are delays in transplant start (>3 weeks following recovery from phase 2 induction), the patient should continue with intensification. If there are still delays in donor procurement following intensification, the patient should not be left without any anti-leukaemia therapy. Depending on the projected duration of delay, either 2 monthly cycles of interim maintenance therapy should be given (as per maintenance phase, with vincristine and steroid, and an intrathecal MTX given each month) OR if anticipated delay is longer than 2 months, patients should instead receive the first cycle of consolidation therapy.

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. Treatment should be agreed in the relevant MDT
8. Assess **creatinine clearance** before prescribing: The initial CrCl before starting methotrexate should ideally be >100 ml/min. Dose reductions must be made if the Cr Cl is <80mls/min.
9. Patients **MUST NOT** receive co-trimoxazole in the week before the first methotrexate infusion and during the intensification/CNS prophylaxis phase.
10. A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative. Review indications for aspirin and NSAIDs, and consider stopping during methotrexate treatment.
11. A fluid space, e.g. pleural effusion or ascites, is potentially dangerous as Methotrexate can

accumulate and cause prolonged toxicity. High dose Methotrexate should not be given in such cases.

DRUG REGIMEN / CYCLE FREQUENCY

T = 0 is the time of the start of the methotrexate infusion

Day 0 (T = -12hr)	**Hydration / Alkalinisation -** Pre methotrexate (starting T= -12 hours; see below).
Day 1 (T=0)	**METHOTREXATE** 3g/m^2 in 500ml 0.9% Sodium Chloride IVI over 24 hours: administer 300mg/m^2 (50ml) over 1 hour, then 2700mg/m^2 (450ml) over the next 23 hours. Infusion must be stopped at 24 hours even if not completed for any reason.
Day 2	**Calcium folinate (Folinic acid) post methotrexate** (starting 36 hours after the start of methotrexate). Continue with fluids and folinic acid rescues until methotrexate level <0.1 micromol/L **PEGYLATED ASPARAGINASE (ONCASPAR®)** 1000IU/m^2 in 100ml 0.9% Sodium Chloride over 1 to 2 hours into a free flowing infusion. **** ONLY for Philadelphia Negative patients ****
Day 14 (T=- 12hr)	**Hydration / Alkalinisation -** Pre methotrexate (starting T= -12 hours; see below).
Day 15 (T=0)	**METHOTREXATE** 3g/m^2 in 500ml 0.9% Sodium Chloride IVI over 24 hours: administer 300mg/m^2 (50ml) over 1 hour, then 2700mg/m^2 (450ml) over the next 23 hours. Infusion must be stopped at 24 hours even if not completed for any reason.
Day 16	**Calcium folinate (Folinic acid) post methotrexate** (starting 36 hours after the start of methotrexate).Continue with fluids and folinic acid rescues until methotrexate level <0.1 micromol/L **PEGYLATED ASPARAGINASE (ONCASPAR®)** 1000IU/m^2 in 100ml 0.9% Sodium Chloride over 1 to 2 hours into a free flowing infusion **** ONLY for Philadelphia Negative patients ****
Day 1 to 28	**IMATINIB** 600mg PO once daily Continue until transplant wherever possible. **** ONLY for Philadelphia Positive patients ****

Intravenous Hydration/Alkalinisation

Start: T = -12 hours.
Fluid: 1000 ml glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 100 mmol added. Following completion of methotrexate infusion, decrease amount of sodium bicarbonate in fluids to 50mmol/L.
Flow rate: 200 ml/hour (or 150 ml/hour if BSA less than 1.6 m^2).

Myeloid group

Duration: Continue fluids during methotrexate infusion (run concurrently with methotrexate,). Administer fluids until 48 hours following completion of methotrexate infusion, or until methotrexate level <0.1 micromol/L.

Sodium Bicarbonate PO 1.5g four times a day + 1.5g PRN for 36 hours. Review regular Sodium Bicarbonate requirements at the end of the Methotrexate infusion, and continue as appropriate until Methotrexate level < 0.1micromol/L.
Dipstick urine every 2 hours to check if pH >7. If pH< 7, give additional Bicarbonate.

Methotrexate Intravenous Infusion

Start: T = 0 (aim to start at 10.00 am).
Run infusion over 24 hours and no longer.
Levels: Check 48hours after the start of the methotrexate infusion, and every 24 hours thereafter until methotrexate level is less than 0.1micromol/L (see below).

Urine Output

Check: Every 4 hours.
Aim: 400 ml/m^2/4 hours (approx. 700 ml over 4 hours).
Furosemide: Administer 20-40 mg to maintain urine output.

Folinic Acid Rescue

Start: 36 hours after the start of methotrexate infusion- T + 36hrs.
Dose: 30 mg IV* every 3 hours for 5 doses, then every 6 hours until methotrexate level is less than 0.1 micromol/L (see below – methotrexate levels).
*Administration: Give intravenous boluses for at least the first 4 doses (i.e. whilst the patient is asleep), change to oral if the patient is compliant and not vomiting.

METHOTREXATE LEVELS

T + 48	If the patient does not suffer nausea or vomiting, IV hydration can be reduced/ stopped but ensure that a combined oral and/or intravenous fluid intake of 6L is maintained. If Methotrexate level < 0.1micromol/L, Folinic Acid and fluids may be discontinued. If Methotrexate level 0.1- 2micromol/L, continue Folinic Acid 30mg every 6 hrs. If Methotrexate level > 2.0micromol/L, continue Folinic Acid 30mg 3 hourly and maintain fluid intake.
T + 72	If Methotrexate level < 0.1micromol/L, Folinic Acid and fluids may be discontinued If Methotrexate level > 2.0micromol/L, continue Folinic Acid 30mg 3 hourly, maintain fluid intake, and discuss with Consultant.
T + 96	Maintain Folinic Acid and fluid intake and until Methotrexate level < 0.1micromol/L

DOSE MODIFICATIONS

The initial creatinine clearance before starting methotrexate should ideally be >100 ml/minute. Dose reductions must be made if the CrCl is <80ml/min before first dose and <50ml/min before the second dose (see below).

METHOTREXATE- Discuss with consultant if required

<table>
<tr><th colspan="2">Renal impairment</th><th colspan="3">Hepatic impairment</th></tr>
<tr><td colspan="2">Pre-dose 1 (Day 1)</td><td>Bili (micromol/L)</td><td>AST</td><td>Dose</td></tr>
<tr><td>CrCl (ml/min)</td><td>Dose</td><td>< 50</td><td>And < 180</td><td>3g/m^2</td></tr>
<tr><td>> 80</td><td>3g/m^2</td><td>51-85</td><td>Or > 180</td><td>2.25g/m^2</td></tr>
<tr><td>50-80</td><td>1.5g/m^2</td><td>> 85</td><td></td><td>Contraindicated</td></tr>
<tr><td>< 50</td><td>omit</td><td colspan="3" rowspan="5">Hypertransaminasaemia and occasionally hyper-bilirubinemia is expected after HD Methotrexate. Elevations can last up to 2 weeks and are not considered toxicities requiring discontinuation. Persistent hyperbilirubinemia and/or Grade 3 / 4 hypertransaminasaemia for > 3 weeks should result in discontinuation of the drug. Reduce dose particularly in patients with concomitantly impaired renal function. Methotrexate is contraindicated in severe hepatic impairment.</td></tr>
<tr><td colspan="2">Pre-dose 2 (Day 15)</td></tr>
<tr><td>CrCl (ml/min)</td><td>Dose</td></tr>
<tr><td>> 50</td><td>3g/m^2</td></tr>
<tr><td>< 50</td><td>omit</td></tr>
<tr><td colspan="2">Carefully monitor CrCl changes during high dose Methotrexate, within and between each cycle.</td></tr>
</table>

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

- Creatinine, U&Es, LFTs

Methotrexate Monitoring:
Before each HD MXT infusion:
- Serum creatinine
- Bilirubin and AST or ALT
- U&Es; Plasma sodium and potassium
- FBC

Fluid balance (at least 4-hourly) and regular weight whilst on HD MXT therapy.
Methotrexate levels as above.

Peg-asparginase monitoring:
- FBC, Coagulation screen.
- Amylase, LFTs, glucose, clotting screen and fibrinogen should be monitored regularly during L-asparginase treatment.

CONCURRENT MEDICATION

ACICLOVIR	200mg PO three times a day continuous
PENTAMIDINE	4mg/kg (max 300mg) in 100ml 0.9% Sodium Chloride IVI over 60 minutes. **Co-trimoxazole MUST BE STOPPED** one week prior to high dose methotrexate
FLUCONAZOLE	50mg PO once daily continuous
Norethisterone	5-10mg PO TDS until platelets >100x 10^9/L with recovery (menstruating women only)
Proton pump inhibitor	As per local formulary Concomitant use is permissible but be aware that it may reduce rate of clearance of HD MTX
Low molecular weight heparin	Thromboprophylaxis in unwell hospitalised adults who have reduced mobility, provided the Plt > 50 x 10^9/L. Prophylaxis or treatment as per local policy

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ANTI-EMETICS

Day 1 - 2	Moderate - High emesis risk
Day 15 - 16	Moderate - High emesis risk
Other days	Low emesis risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Main side effects experienced during intensification: nausea and vomiting, myelosupressions, infections, liver toxicity and hair loss, renal impairment, mucositis.

Methotrexate:

Renal damage, Hepatotoxicity, Nausea/vomiting, Interstitial pneumonitis (cough, dyspnoea, fever), Stomatitis, diarrhea, Hair loss.

Glucarpidase – Reversal Agent

NHS England will fund Glucarpidase (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m2)

- Who develop significant deterioration in renal function (>1.5x ULN and rising, or the presence of oliguria) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

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®):

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/m2 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.

INTERACTIONS

HD methotrexate:

- Patients MUST NOT receive co-trimoxazole in the week before high dose MTX therapy, and during the intensification phase. Prescribed pentamidine as an alternative for PJP prophylaxis.
- Drugs which compromise renal function e.g. Aminoglycosides can decrease clearance of methotrexate and lead to systemic toxicity.
- Avoid concurrent use of Non-steroidal anti-inflammatory (NSAIDs) including salicylates and sulphonamides. Review indications for aspirin and NSAIDs and consider stopping during methotrexate treatment.
- Large doses of penicillin may interfere with the active renal tubular secretion of methotrexate. Tazocin should NOT be used during high dose methotrexate administration or rescue. Consider using meropenem or other alternative.

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