UKALL 14 Intensification/CNS Prophylaxis Therapy

This is a clinical trial protocol intended for off-trial use.

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult patients (aged 25–65 years)** with newly diagnosed, previously untreated acute lymphoblastic leukaemia (ALL) following Phase 2 Induction Therapy	C91	00876a	N/A

*This applies to post 2012 indications only

TREATMENT:

Table 1: UKALL14 treatment schedule

Phase 1 Standard induction	Phase 2 Standard induction	Intensification / CNS Prophylaxis	Consolidation Phase Cycle 1	Consolidation Phase Cycle 2	Consolidation Phase Cycle 3	Consolidation Phase Cycle 4	Maintenance

Treatment is administered as described in the treatment table below. The treatment cycle is 28 days.

**It may sometimes be used in patients ≥ 19 years with Philadelphia Chromosome positive acute lymphoblastic leukaemia.

Patients being treated for ALL require complex inpatient care in a designated cancer centre with comprehensive multidisciplinary team (MDT) availability.

Note:

- This regimen may be omitted if a myeloablative transplant is to be carried out, but if there are delays in transplant start (> 3 weeks following recovery from Induction Phase 2), the patient should continue with per-protocol intensification.
- If there are still delays, in conjunction with the transplant centre, further treatment should be agreed.
    - Depending on the projected duration of delay, either 2 monthly cycles of interim maintenance therapy should be given (as per maintenance phase of this protocol, with vinCRIStine and steroid and an intrathecal methotrexate (MTX) given each month)

      OR

    - if anticipated delay is longer than 2 months, patients should instead receive the first cycle of Consolidation Therapy **(Refer to NCCP Regimen 00877 UKALL 14 Consolidation Phase Cycle 1)**

- Treatment typically begins after recovery from Induction Phase 2 **(Refer to NCCP Regimen 00875 UKALL 14 Phase 2 Standard Induction Therapy).**
    - Haematopoietic recovery from Phase 2 Induction i.e. when ANC > 0.75 x 10^9/L and Platelets > 75 x 10^9/L and confirm remission by morphological bone marrow examination including Minimum Residual Disease (MRD) examination.

Facilities to treat anaphylaxis MUST be present when systemic anticancer treatment (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate
1 and 15	Methotrexate[a]	300mg/m^2	IV infusion	500mL NaCl 0.9% over 1 hour
1 and 15	Methotrexate[a]	2700mg/m^2	IV infusion	1000mL NaCl 0.9%l over 23 hours[b]
2 and 16	Folinic acid[c]	15mg/m^2	IV infusion	100mL NaCl 0.9% over 10 minutes. Commence 36 hours after the start of 1st methotrexate infusion and repeat every 3 hours for 4 doses and then dose according to methotrexate level (Reference Table 2) until methotrexate level is <0.1 micromol/L
2 and 16	PEG-asparaginase **(Philadelphia negative patients** ONLY)	1000 International Units/m^2	IV infusion	100mL NaCl 0.9% over 2 hours
1-28	Imatinib **(Philadelphia positive patients** ONLY)	600mg[d]	PO	n/a
[a]See table 1: Guidance for methotrexate administration below				
[b]Infusion must be stopped after 24 hours even if not completed for any reason.				
[C]See Table 2 Calculation of Folinic Acid Rescue on the basis of methotrexate levels below				
[d]Patient may require 400mg dose if 600mg not tolerated				

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Table 2: Guidance for methotrexate administration

Methotrexate:

Hydration and Alkalinisation regimens are required with methotrexate. See below for suggested **or** Refer to local policy.

Adequate hydration and urine output are essential for the rapid clearance of methotrexate

- GFR to be calculated prior to administration of methotrexate infusion**.** Consider formal measurement (24 hours collection) of GFR if there is clinical concern.
- Consider formal measurement (24 hours collection) of creatinine clearance before the 2nd infusion if there is delayed methotrexate excretion after the first course.

- Commence pre-hydration with sodium bicarbonate containing infusions at 125mLs/m^2/hr at least 6 hours prior to methotrexate infusion.
- **Hydration** with at least 3L/m^2/24 hours of **IV fluids** throughout treatment is essential until the methotrexate level is <1x 10^{-7}M (0.1micromol/L)
- Urine pH should be ≥ 7.0 prior to commencement and during the methotrexate and folinic acid rescue. Check urine pH at regular intervals (6 hourly)
- **Alkalinisation** can be achieved with 50mmol of sodium bicarbonate over 8 hours in 1000mL 0.9% NaCl. If required, the sodium bicarbonate content may be increased to 80mmol in 1L (this should not be given over less than 6 hours). In exceptional circumstances, doses higher than 80mmol may be required, discuss with consultant.
  (This volume administered for alkalinisation is included in the total volume of hydration.)
  - Check urine pH at regular intervals (6 hourly)
  - If the target pH is not reached adjust the sodium bicarbonate concentration to maintain the urinary pH ≥ 7.0
- **Potassium** should be supplemented according to the local policy.
- Check **fluid balance** at regular intervals (4 hourly) through each day. (Furosemide may be administered if fluid output falls below 400mLs/m^2 in a 4-hour period).
- **Methotrexate levels** must be taken 48 hours, 72 hours, 96 hours and 120 hours as appropriate after commencement of the initial methotrexate infusion (book levels in advance with lab).
- Continue alkalinisation, hydration and folinic acid rescue (Table 3) until methotrexate level is <1x 10^{-7}M (0.1micromol/L)

Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mLs or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide. If furosemide is given, monitor pH for 2 hours post dose as this can cause pH to drop. If a drop in pH persists post 2 hours, increase alkinisation fluid rate from 8 hours to 6 hours until resolved.

Table 3: Calculation of Folinic Acid Rescue on the basis of Methotrexate Levels

Time after starting Methotrexate infusion	Methotrexate Plasma Concentration[a] (micromol/L)				
	<0.1[b]	0.1-2	2-20	20-100	>100
48 hours	No folinic acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours
72 hours	No folinic acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
96 hours	No folinic acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
120 hours[c]	No folinic acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours

[a] If glucarpidase is required as rescue for methotrexate toxicity, refer to the product literature for details.

[b] No extra folinic acid is required provided MTX levels are below 0.1 micromol/litre at 48h.

[c] At time points after 120h folinic acid administration should be continued as recommended for 120h.

ELIGIBILITY:

- Indication as above
- Aged ≥ 25 and ≤ 65 years old with acute lymphoblastic leukaemia **OR** ≥ 19 and ≤ 65 years old with Philadelphia Chromosome positive acute lymphoblastic leukaemia.

EXCLUSIONS:

- Hypersensitivity to methotrexate, folinic acid, PEG-asparaginase, imatinib or any of the excipients
- Refer to NCCP Regimen 00874 UKALL14 Phase 1 Standard Induction Therapy for exclusions

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- Refer to UKALL14 v 12 trial protocol for full details
- Ensure all previous pre-assessments as per Phase 1 Standard Induction have been completed
- FBC, liver and renal profile
    - Initial CrCl before starting methotrexate should ideally be >100mL/min. Dose reductions must be made if CrCl is <80mL/min
- Amylase, blood glucose, coagulation screen including fibrinogen

Regular tests:

- Refer to UKALL14 v 12 trial protocol for full details
- Refer to table 2 and 3 above for further details on regular tests for the administration of high dose intravenous methotrexate
- FBC, renal and liver profile
- Amylase, blood glucose, coagulation screen including fibrinogen

Disease monitoring:

Disease monitoring (including MRD by flow and molecular methods) should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Further detailed information on managing dose modifications can be found in the UKALL14 v12 trial protocol.

Renal and Hepatic Impairment:

- 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 Table 4 below).
- Carefully monitor CrCl changes during high dose methotrexate, within and between each cycle.

Table 4: Recommended dose modification in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="3">Hepatic Impairment</th></tr>
<tr><td rowspan="5">Methotrexate:</td><td colspan="2">Pre Cycle 1</td><td rowspan="2">Bilirubin (micromol/L)</td><td rowspan="2">AST</td><td rowspan="2">Dose</td></tr>
<tr><td>CrCl (mL/min)</td><td>Dose</td></tr>
<tr><td>>80</td><td>100%</td><td rowspan="3"><50</td><td rowspan="3">And <180</td><td rowspan="3">100%</td></tr>
<tr><td>50-80</td><td>50%</td></tr>
<tr><td><50</td><td>Omit</td></tr>
<tr><td rowspan="4">Methotrexate:</td><td colspan="2">Pre Cycle 2</td><td rowspan="2">51-85</td><td rowspan="2">Or >180</td><td rowspan="2">75%</td></tr>
<tr><td>CrCl (mL/min)</td><td>Dose</td></tr>
<tr><td>>50</td><td>100%</td><td rowspan="2">>85</td><td rowspan="2"></td><td rowspan="2">Contraindicated</td></tr>
<tr><td><50</td><td>Omit</td></tr>
<tr><td>Imatinib</td><td colspan="2">Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients, caution is recommended. The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy</td><td colspan="3">Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated.</td></tr>
<tr><td>PEG-asparaginase</td><td colspan="2">No dose adjustment is needed

Haemodialysis: no need for dose adjustment is expected</td><td colspan="3">Consider withholding if rising total bilirubin.

Definitely withhold if total bilirubin > 50.
For severely abnormal transaminases, discuss with treating clinician.</td></tr>
<tr><td colspan="6">Methotrexate: Renal and hepatic - UKALL 14v12 trial protocol
Imatinib: Renal and hepatic – Product SmPC
PEG-asparaginase: Renal - Giraud et al 2023, hepatic - as agreed with clinical reviewer/clinical advisory group</td></tr>
</table>

Management of adverse events:

Table 5: Dose modification schedule based on adverse events

Drug	Adverse reactions			Recommended dose modification
Imatinib	**Bilirubin**		**Liver Transaminases**	
	> 3 x ULN	or	> 5 x ULN	Hold until bilirubin < 1.5 x ULN and transaminase levels < 2.5 x ULN and then resume at reduced dose: • 400mg to 300mg or • 600mg to 400mg
	Severe non-haematological toxicity			Withhold treatment until resolved. Resume treatment depending on the initial severity of the event.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting available on the NCCP website

Methotrexate: Moderate **(Refer to local policy).**
Imatinib: Moderate to high* **(Refer to local policy).**

*Based on clinical experience, the emetogenic potential of imatinib may be regarded as moderate as opposed to moderate to high.

For information:

Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) available on the NCCP website

PREMEDICATIONS:

- Premedicate patients as per table 6 below prior to administration of PEG-asparaginase to decrease the risk and severity of both infusion and hypersensitivity reactions.

Table 6: Suggested pre-medications prior to PEG-asparaginase infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60 minutes prior to infusion
Chlorphenamine*	10mg	IV bolus at least 30 minutes prior to infusion
* This can be given +/- hydrocortisone 100mg IV		

OTHER SUPPORTIVE CARE:

- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy). Consider interactions between methotrexate and co-trimoxazole. If co-trimoxazole cannot be avoided, cease PJP prophylaxis at least 48 hours prior to methotrexate infusion and recommence upon clearance of methotrexate at end of intensification phase.**
- Norethisterone (menstruating women only) **(Refer to local policy)**
- Proton pump inhibitor (PPI) **(Refer to local policy)**

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information

REFERENCES:

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2. NHS Thames Valley. ML.49 ALL intensification CNS Prophylaxis. Last updated Oct 2019. Accessed 14.01.2025. Available at: https://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-49-all-intensification-cns-prophylaxis.pdf
3. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
5. Methotrexate Summary of Product Characteristics. Last updated: 10/06/2025. Accessed September 2025. Available at: https://assets.hpra.ie/products/Human/22087/Licence_PA0822-206-002_10042025112938.pdf

6. Imatinib (Glivec®) Summary of Product Characteristics. Last updated: 04/08/2025. Accessed September 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/imatinib-teva-epar-product-information_en.pdf
7. Pegasparaginase (Oncaspar®) Summary of Product Characteristics. Last updated: 09/07/2024. Accessed September 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/oncaspar-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/10/2025		Prof. Mary Cahill, Dr. Robert Henderson, Dr Janusz Krawczyk

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