Cladribine +/- Rituximab

INDICATIONS

Licensed / NHS funded: **HAIRY CELL LEUKAEMIA (HCL)** [ICD-10 code: C91]

- Newly diagnosed or relapsed/refractory HCL, including hairy cell leukaemia variant (HCL-V) as monotherapy (within the marketing license) or in combination with rituximab (in line with the British Society for Haematology guidelines).

Unlicensed*/ Unfunded: **LOW-GRADE NON-HODGKIN LYMPHOMA (NHL)** [ICD-10 codes: 82, 85, 88]

- Relapsed/refractory indolent NHL, in combination with rituximab [Ensure local funding for cladribine is agreed].

Unlicensed* / NHS funded: **HISTIOCYTOSIS** [ICD-10 codes: C76, C96]

- Non-Langerhans or Langerhans cell histiocytosis [NHSE funded following recommendation from National Histiocytosis Advisory Panel for individual patients].

*Local governance policy should be followed for unlicensed (off-label) use.

For advanced systemic mastocytosis (ASM) – refer to the Myeloid protocol [Link to follow]

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Ensure histology/flow cytometry is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, bone marrow aspirate and trephine.
3. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, HbA1c, Igs, β_2 microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV, HTLV-1, glucose 6-phosphate dehydrogenase (G6PD) (when indicated, [H.8]), group and save.
4. Send a "group and save" sample to transfusion and ensure patient has been flagged to blood bank for the requirement of **irradiated blood products** for all future transfusions. Refer to [Guidelines for the use of blood components in adult haematology].
5. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or had a hysterectomy.
6. ECG +/- ECHO - if clinically indicated.
7. Record performance status [ECOG].
8. Record vital signs, height and weight.
9. Consent and counselling - 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 prior to treatment.
10. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Assess and document tumour lysis risk as part of pre-assessment. Patients should be adequately hydrated before and after each cycle administration. Refer to the Tumour Lysis Syndrome in Adults protocol [H.8].
12. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Day(s)	Drug	Dose	Route	Administration details
1–5	**CLADRIBINE (LITAK®)**	**0.14 mg/kg**	**SC**	Subcutaneous injection
CYCLE FREQUENCY & TREATMENT DURATION: ▪ HCL: usually once only ▪ NHL: every 28 days for 2–6 cycles ▪ Histiocytosis: 2 cycles at full dose (as above) every 28 days, then restaged (with CT NCAP/MRI) for up to 6 cycles				

Day	Drug	Dose	Route	Administration details
1	Paracetamol Hydrocortisone Chlorphenamine	1000 mg 100 mg 10 mg	PO IV IV	≥ 30 minutes before rituximab
1	**RITUXIMAB**	**375 mg/m²**	**IV**	In 500 mL sodium chloride 0.9% [Refer to [Nursing Care Plans: Rituximab infusion rates], max. rate 400mg/hour]. Patients should be observed for 30 minutes before the start of other infusions. If first dose well tolerated, consider rapid infusion rituximab rate from cycle(s) 2 onwards.
CYCLE FREQUENCY & TREATMENT DURATION: ▪ HCL: weekly for 4 weeks ▪ NHL (CD20+positive): every 28 days for 2–6 cycles				

CONCURRENT MEDICATIONS

Antiviral prophylaxis	Aciclovir 200mg three times a day for the duration of treatment and **for 6 months afterwards**, or until adequate neutrophil and lymphocyte recovery.
PJP prophylaxis	Co-trimoxazole 480mg daily on Mon/ Wed/ Fri, started after the 5-day course of cladribine treatment, to minimize confusion about cladribine-, or co-trimoxazole-induced rash and continued **for 6 months afterwards**, or until adequate neutrophil and lymphocyte recovery. Consider reducing the dose to 480mg twice weekly during neutropenic periods. Pentamidine can be considered for patients who are intolerant or allergic to co-trimoxazole.
Antifungal prophylaxis	Fluconazole 50 mg daily for the duration of treatment
TLS prophylaxis*	Hydration – encourage oral fluids only. *Uric acid lowering medications are not usually required (allopurinol should be avoided – see INTERACTIONS section below). Refer for full details to "Tumour Lysis Syndrome in Adults" protocol [H.8].
Anti-emetics*	*Minimal emetic risk: no routine prophylaxis required
G-CSF prophylaxis*	*Consider for Grade 1 neutropenia and administer for grade ≥ 2, then as secondary prophylaxis at the Consultant discretion, for example, filgrastim 0.5 MU/kg/day, starting from day 9 for 5 days.

(*) indicates optional concurrent medications

CONTRAINDICATIONS

Hypersensitivity to active ingredients and excipients. Active severe infections. Refer for full details to individual medications Summary of Product Characteristics (SmPCs).
Note LITAK® is contraindicated in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 mL/min) or with moderate to severe hepatic impairment (Child-Pugh score > 6).

INVESTIGATIONS

Before each cycle: FBC, renal and liver profiles

RE-STAGING

After count recovery and at least 4 months after completing cladribine therapy, consider bone marrow and ultrasound or CT.

TREATMENT MODIFICATIONS

Discuss all grade 3 or 4 toxicities with the Consultant.

CLADRIBINE

Haematological toxicities:
▪ Further cycles should only be delayed if neutrophils < 0.2 x 10^9/L in a patient whose initial neutrophil count was > 0.5 x 10^9/L and may be resumed when the neutrophil count has returned to pre-dose levels. G-CSF support may be initiated during treatment as appropriate. ▪ Thrombocytopenia – discuss with the Consultant. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice may be required. ▪ No dose reductions or delays should be made for anaemia.

Renal impairment	**Hepatic impairment**
GFR > 50 mL/min 100% dose	Mild: no need for dose adjustment is expected
GFR ≤ 50 mL/min not recommended	Moderate and severe or Child-Pugh B/C: not recommended

DRUG INTERACTIONS

Allopurinol	Both allopurinol and cladribine are associated with skin rashes. Consider avoiding the combination.
Corticosteroids	Concomitant use should be avoided due to increased risk of infections.
Anti-hypertensive medications	Since hypotension may occur during rituximab administration, consider withholding anti-hypertensive medication(s) 12 hours prior to infusion.

EXTRAVASATION RISK

Cladribine: neutral
Rituximab: neutral

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Cladribine:

- Very common: neutropenia, anaemia, thrombocytopenia, infection, fever, skin rashes, lethargy, anorexia, fever, nausea, vomiting, headache.
- Risk of secondary malignancy.

Rituximab:

- Rituximab may cause infusion related reactions (IRRs) or severe cytokine release syndrome, characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema.
- Hepatitis B reactivation – following rituximab administration – see pathway for treatment and management of HBV positive patient [LPW.21].
- Generic rituximab (IV formulation) is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card scheme.
- Maintenance treatment is associated with an increase in infections most of which are manageable as an outpatient.

TREATMENT RELATED MORTALITY

1–5%

REFERENCES

1. Randomized Phase II Study of First-Line Cladribine With Concurrent or Delayed Rituximab in Patients with Hairy Cell Leukaemia. J Clin Oncol. 2020 May 10;38(14):1527-1538. Doi:10.1200/JCO.19.02250.
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5. LIPOMED GmbH. LITAK 2mg/ml solution for injection. Summary of Product Characteristics (SmPC). Last updated 25/01/2024. Available at https://www.medicines.org.uk/emc/ <Last accessed 16/09/2024>
6. Celltrion Healthcare UK Limited. Truxima® 500 mg concentrate for solution for infusion. Summary of Product Characteristics (SmPC). Last updated 13/12/2022. Available at https://www.medicines.org.uk/emc/ <Last accessed 16/09/2024>
7. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229

REVIEW

Name	Revision	Date	Version	Review date
NSSG Lymphoma Group	Annual protocol review	May 2017	3.7	
NSSG Lymphoma Group	Annual protocol review	May 2019	3.8	May 2021
Stephen Booth and Sara Castro	Clarification of Rituximab schedule and addition of Rituximab to first line HCL treatment	Oct 2020	3.9	Oct 2021
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, NSS Lymphoma&CLL Group	Indications, contraindications, drug regimen [IV cladribine removed], concurrent medications [allopurinol not required], interactions, adverse reactions updated. General formatting. Annual Protocol review.	September 2024	4.0	September 2027