Pentostatin +/- 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*: **T-CELL PROLYMPHOCYTIC LEUKEMIA (T-PLL)** [ICD-10 code: C91]

- T-PLL in patients who are refractory to alemtuzumab. Can be combined with alemtuzumab. *Ensure compliance with treating Trust's governance framework and local funding is agreed.

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, 15	Pre-hydration: Sodium Chloride	0.9%	IV	500 mL over 1 hour
1, 15	**PENTOSTATIN**	**4 mg/m²**	**IV**	Slow bolus injection
1, 15	Post-hydration: Sodium Chloride	0.9%	IV	500 mL over 1 hour
CYCLE FREQUENCY: 28 days				
TREATMENT DURATION: until a **maximum** response (for example, normalisation of blood counts) has been achieved then for a further 2 doses. **10 doses normally required (5 cycles)**. If partial response (based on blood counts) not achieved after 4 doses, pentostatin should be discontinued.				

Day(s)	Drug	Dose	Route	Administration details
1, 15	Paracetamol Hydrocortisone Chlorphenamine	1000 mg 100 mg 10 mg	PO IV IV	≥ 30 minutes before rituximab
1, 15	**RITUXIMAB** [HCL indication only]	**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: 28 days (when given on days of pentostatin)*				
TREATMENT DURATION: up to 6–8 doses (3-4 cycles)				

*Alternatively, rituximab can be given weekly, starting after the pentostatin treatment has been completed, for up to 6–8 doses.

CONCURRENT MEDICATIONS

Antiviral prophylaxis	Aciclovir 200mg three times a day for 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 for duration of treatment and **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
Anti-emetics [Days 1 & 15: Low risk]	▪ Metoclopramide 10-20mg TDS on days 1 and 15. For breakthrough nausea or vomiting: 10-20mg TDS when required. For alternative options, refer to [TVCA Anti-emetic guideline].
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].
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 2 and 16 for 5-7 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).

INVESTIGATIONS

Before each pentostatin dose: FBC, renal and liver profiles

RE-STAGING

Repeat bone marrow biopsy 6 months after treatment finished.

TREATMENT MODIFICATIONS

Discuss all grade 3 or 4 toxicities with the Consultant.

PENTOSTATIN

Haematological toxicities:
▪ Further doses 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 > 59 mL/min: 100% dose GFR 40-59 mL/min: 75% dose GFR 35-39 mL/min: 50% dose GFR < 35 mL/min: not recommended	No formal dose adjustment required. However, caution is advised.

DRUG INTERACTIONS

Allopurinol	Both allopurinol and pentostatin are associated with skin rashes. Consider avoiding the combination.
Anti-hypertensive medications	Since hypotension may occur during rituximab administration, consider withholding anti-hypertensive medication(s) 12 hours prior to infusion.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Pentostatin:

- Temporary myelosuppression [very common (>10%): leucopenia, thrombocytopenia, anaemia, blood disorder, eosinophilia, hypochromic anaemia, pancytopenia] and a more prolonged immunosuppression.
- Skin changes (dry, itchy, acne)
- Liver, renal, lung damage
- Hair loss, lethargy, anorexia
- Fever, headache, nausea and vomiting

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.

EXTRAVASATION RISK

Pentostatin: neutral
Rituximab: neutral

TREATMENT RELATED MORTALITY

3–5% (depends on indication)

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
NSSG Lymphoma Group	Annual protocol review	May 2017	1.5	
NSSG Lymphoma Group	Annual protocol review	May 2019	1.6	May 2021
Sara Castro, Advanced Haematology Pharmacist	Annual Protocol review	July 2021	1.7	May 2023
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, NSSG Lymphoma &CLL Group	Indications, contraindications, drug regimen, concurrent medications [allopurinol not required], interactions updated. General formatting. Annual Protocol review.	September 2024	2.0	September 2027