

Cladribine 5 day and riTUXimab Therapy¹

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment for adult patients with relapsed or partially responsive Hairy Cell Leukaemia	C91	00531a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Cladribine is administered on days one to five of a five day cycle only. RiTUXimab is commenced one week after finishing cladribine therapy. RiTUXimab is administered every seven days for 6 weeks.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Week
1-5	cladribine	0.14mg/kg	SC ¹	n/a	1
One week break from treatment					
1	riTUXimab	375mg/m ²	IV infusion ² Observe post infusion ³	500ml NaCl 0.9% at a maximum rate of 400mg/hr ^{2,4,5}	3-8 ⁶
¹ Note: In individual cases where there is local reaction or contra-indication to SC and following approval by Consultant cladribine may be administered as IV Infusion over two hours (Note that this is an unlicensed method of administration).					
² The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Subsequent infusions can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr. Development of an allergic reaction may require a slower infusion rate. See Hypersensitivity/Infusion reactions under Adverse Effects/Regimen Specific Complications below. Any deviation from the advised infusion rate should be noted in local policies.					
³ Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.					
⁴ RiTUXimab should be diluted to a final concentration of 1-4mg/ml.					
⁵ Rapid rate infusion schedule ¹ See NCCP guidance here If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of riTUXimab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions. Initiate at a rate of 20% of the total dose for the first 30 minutes and then 80% of the dose for the next 60 minutes (total infusion time of 90 minutes). If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to riTUXimab, should not be administered the more rapid infusion.					
⁶ Treatment may be continued for a further two weeks at the discretion of the prescribing consultant (total eight cycles of riTUXimab)					

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ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to cladribine, ritUXimab or any of the excipients or to murine proteins
- Creatinine Clearance \leq 50ml/min
- Moderate to severe hepatic impairment (Child–Pugh Score $>$ 6)
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- Bone marrow aspirate, biopsy and immunophenotyping
- Cardiac function if clinically indicated
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV CMV, EBV, VZV and HSV.

*See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC weekly during treatment and for up to 8 weeks after therapy
- Renal and liver profile and LDH as clinically indicated
- Creatinine clearance using Cockcroft Gault equation

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Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s, as directed by the supervising Consultant.

Bone marrow reassessment post cladribine treatment should generally be delayed for 4 to 6 months to allow for delayed marrow recovery that can be associated with cladribine.

DOSE MODIFICATIONS:

- No dose reductions of ritUXimab are recommended
- Any dose modification should be discussed with a Consultant

Renal and Hepatic Impairment:

Table 1: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment	Hepatic impairment
Cladribine	Contraindicated in patients with moderate to severe renal impairment (creatinine clearance \leq 50 ml/min)	Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh score $>$ 6)
RiTUXimab	No dose reductions necessary	No dose reductions necessary

Management of adverse events:

Table2: Dose modification schedule of ritUXimab based on adverse events

Adverse reactions	Discontinue	Recommended dose modification
Severe infusion related reaction (e.g dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence		Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x -ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate.
Second occurrence	Consider discontinuing treatment	Consider coverage with steroids for those who are not already receiving steroids.
Mild or moderate infusion-related reaction		Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Cladribine: Minimal (**Refer to local policy**)

RiTUXimab: Minimal (**Refer to local policy**)

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PREMEDICATIONS: Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of ritUXimab.

Suggested pre-medications:

Chlorpheniramine 10mg IV + paracetamol 1gram PO.

Consider hydrocortisone 100mg-200mg IV 30 minutes prior to therapy in patients not receiving glucocorticoid containing chemotherapy.

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis (**Refer to local policy**)
- PJP prophylaxis (**Refer to local policy**)*
- Anti-viral prophylaxis (**Refer to local policy**)*
- Anti-fungal prophylaxis (**Refer to local policy**)
- All patients being treated with cladribine should receive irradiated blood products (**Refer to local policy**)
- Contraceptive measures for women of child-bearing potential during therapy and for at least 6 months after cessation of therapy.

*Note : Recommended that the use of concomitant drugs should be minimised during cladribine infusions as patients often develop rashes.

Co-trimoxazole and aciclovir should be started once treatment is completed

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Fever** of unknown origin frequently occurs in patients treated for hairy cell leukaemia and is manifested predominantly during the first 4 weeks of therapy
- **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.

Cladribine

- Cladribine is an antineoplastic and immunosuppressive substance that can induce considerable toxic adverse reactions, such as myelo- and immunosuppression, long-lasting lymphocytopenia, and opportunistic infections. Patients undergoing treatment with cladribine should be closely monitored for signs of haematological and non-haematological toxicities.
- **Progressive multifocal leukoencephalopathy (PML):** Cases of PML, including fatal cases, have been reported with cladribine. PML diagnosis has been reported 6 months to several years after treatment with cladribine. An association between cladribine and prolonged lymphopenia was reported in several of these cases. Consider PML in the differential diagnosis for patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected, the patients should not receive further treatment with cladribine

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- **Secondary malignancies:** Like other nucleoside analogues, treatment with cladribine is associated with the occurrence of second malignancies. Therefore, regular monitoring of patients treated with cladribine is required.
- **Haematological toxicity:** During the first month following treatment, myelosuppression is most notable and red blood cell or platelet transfusions may be required. An increased incidence of opportunistic infections is expected during and for 6 months following therapy with cladribine. Careful and regular monitoring of peripheral blood counts is essential during and for 2 to 4 months following treatment with cladribine.
- **Fertility:** Men being treated with cladribine should be advised not to father a child up to 6 months after treatment. Women of childbearing potential must use effective contraception during treatment with cladribine and for 6 months after the last cladribine dose.

RiTUXimab

- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first infusion (**Refer to local policy**). RiTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, pruritis, sneezing, cough, fever or faintness.
- **Severe Cytokine Release syndrome:** Usually occurs within 1 to 2 hours of initiating the first infusion of riTUXimab. This syndrome may be associated with some features of cytokine release/tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death.
 - Pulmonary interstitial infiltrates or oedema visible on chest x-ray may accompany acute respiratory failure.
 - For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.
- **Hepatitis B Reactivation:** Has been reported in patients receiving riTUXimab including fulminant hepatitis with fatal outcome.
- **Severe Mucocutaneous Reactions:** These include Steven Johnson syndrome and toxic epidermal necrolysis. Discontinue riTUXimab in patients who develop a severe mucocutaneous reaction. The safety of readministration has not been determined.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.
- **Progressive multifocal leukoencephalopathy (PML):** Use of riTUXimab may be associated with an increased risk of PML. Patients must be monitored for any new or worsening neurological symptoms. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of rituximab must be permanently discontinued.
- **Infections:** RiTUXimab should not be administered to patients with an active, severe infection. Caution should be exercised when considering the use of riTUXimab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.

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- **Vaccines:** Vaccination with live virus vaccines is not recommended whilst on ritUXimab. Patients treated with ritUXimab may receive non-live vaccinations

DRUG INTERACTIONS:

- Due to a potential increase of haematological toxicity and bone marrow suppression, cladribine must not be used concomitantly with other myelosuppressive medicinal products.
- Corticosteroids have been shown to enhance the risk of severe infections when used in combination with cladribine and should not be given concomitantly with cladribine.
- Currently, there is limited data on possible drug interactions with ritUXimab.
- Antihypertensives: Additive effect of hypotension during ritUXimab infusion. Consider withholding antihypertensives 12 hours before and during ritUXimab infusion.
- There is a diminished response to vaccines and increased risk of infection with live vaccines. Vaccination with live virus vaccines is not recommended for patients on ritUXimab therapy.
- Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3AR inhibitors/inducers.

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Version	Date	Amendment	Approved By
1	23/11/2018		Dr Kamal Fadalla
2	01/03/2021	Amended emetogenic potential and adverse effects (hepatitis B reactivation)	Dr Kamal Fadalla

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱ This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be aware of their responsibility in communicating any relevant information to the patient and also in ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

Further details on the Cancer Drug Management Programme is available at; <http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/>

ⁱⁱ The rapid infusion is an unlicensed means of administration of rituximab for the indications described above, in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

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