Regimen Monograph

A - Regimen Name

CVP(PO)+R Regimen

Cyclophosphamide (oral)-VinCRIStine-Prednisone-riTUXimab

Disease Site

Hematologic
Lymphoma - Non-Hodgkin's Low Grade

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

Treatment of follicular lymphoma or other indolent histology, CD20-positive B-cell lymphoma (**excluding** small lymphocytic lymphoma (SLL), or chronic lymphocytic leukemia (CLL)), in patients who:

- Have not received previous treatment with rituximab for indolent B-cell lymphoma
- Have previously received rituximab (including combination rituximab-chemotherapy and/or rituximab monotherapy or maintenance rituximab) and have sustained a response and remained disease-free for at least 6 months after the last dose of rituximab

Refer to the NDFP eligibility forms for detailed funding criteria.

Supplementary Public Funding

prednisone
ODB - General Benefit (prednisone) (ODB Formulary)

riTUXimab
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC in Combination with Chemotherapy - Indolent B-cell Lymphoma) (NDFP Website)

riTUXimab
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - Retreatment - Indolent Lymphoma) (NDFP Website) (in combination with chemotherapy)

cyclophosphamide
ODB - General Benefit (cyclophosphamide - oral tablets) (ODB Formulary)

riTUXimab (subcut)
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC in Combination with Chemotherapy - Indolent B-cell Lymphoma)

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B - Drug Regimen

Note: Different rituximab products are NOT INTERCHANGEABLE.

Cycle 1: All patients must receive their first dose of rituximab by IV infusion

prednisone[1]	100 mg	PO daily	Days 1 to 5
(Outpatient prescription in multiples of 50mg tablets)			
riTUXimab	375 mg /m²	IV	Day 1
vinCRIStine	1.4 mg /m²	IV (maximum 2 mg)	Day 1
cyclophosphamide	400 mg /m²	PO daily	Days 1 to 5
(Outpatient prescription in multiples of 25mg & 50mg tablets)			

Cycle 2 and onwards: (For a usual total of 6-8 cycles, including initial IV rituximab cycle(s))

riTUXimab	375 mg /m²	IV	Day 1

OR

Rituximab subcutaneous:

The subcutaneous formulation must only be given at the second or subsequent cycles, and only after at least 1 full rituximab IV dose.

riTUXimab (subcut)	1400 mg	Subcut	Day 1

Plus CVP(PO) Chemotherapy

prednisone[1]	100 mg	PO daily	Days 1 to 5
vinCRIStine	1.4 mg /m²	IV (maximum 2 mg)	Day 1
cyclophosphamide	400 mg /m²	PO daily	Days 1 to 5

(1) On Day 1 to be given as part of premedication before riTUXimab

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C - Cycle Frequency

REPEAT EVERY 21 DAYS
For a usual total of 6-8 cycles in the absence of unacceptable toxicity or disease progression

For patients who responded to induction therapy, and were rituximab-naïve prior to induction, refer to maintenance rituximab regimen - RITU(MNT) or RITU(MNT-SC).

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal
Consider prophylaxis daily for cyclophosphamide PO

Other Supportive Care:

- Also refer to CCO Antiemetic Recommendations.
- **Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.
- If high volume disease, consider prophylaxis for tumour lysis.

Premedication (prophylaxis for infusion reactions):

Administer at least 30 minutes prior to rituximab:

- Oral antipyretic (e.g. acetaminophen)
- H1-receptor antagonist (e.g. diphenhydramine)
- Give day 1 prednisone as part of pre-medication before rituximab.
- In patients receiving **subcut rituximab** who experienced adverse effects with pre-medications, the omission of pre-medications can be considered.

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E - Dose Modifications

See premedication and monitoring sections for supportive care, screening and monitoring recommendations. Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Toxicity	Vincristine[1] (% previous dose)	Cyclophosphamide[1] (% previous dose)	Rituximab IV or Subcut[1,2](% previous dose)
Grade 4 hematological, febrile neutropenia, bleeding	100%	75% or G-CSF for low ANC	100%
Grade 3 non-hematological toxicity	100%	75%	100% or delay
Neurotoxicity	***Mild***: 67%; ***Moderate***: Hold until recovery, then ↓ 50%; ***Severe***: Discontinue	100%	100%

Cystitis	100%	Hold until resolution	100%
Grade 4 organ toxicity	Discontinue	Discontinue	Discontinue
• Severe mucocutaneous toxicity • Serious/life-threatening cardio-pulmonary events • Reactivation of tuberculosis or hepatitis B • Evidence of active hepatitis • PML / RPLS	Discontinue	Discontinue	Discontinue

[1]Prior to retreatment, major organ toxicity should have recovered to ≤ grade 2, ANC to ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L.
[2]Missed or delayed doses may be administered at a later time point, based on physician's discretion

Management of Rituximab Administration-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Rituximab:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • Once symptoms have resolved, restart at 50% of the IV rate at which the IR occurred.	• Re-challenge at 50% of the IV administration rate at which the IR occurred and with pre-medications. • Consider adding oral montelukast ± oral acetylsalicylic acid.

3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Consider clinical benefit and risks of further treatment. Consider patient factors, severity and nature of the IR and availability of suitable alternative treatment. • Consider desensitization for patients with recurrent reactions despite pre-medications and a slower infusion rate.

Hepatic Impairment

Bilirubin	Vincristine* (% previous dose)	Cyclophosphamide (% previous dose)	Rituximab
1 – 2 x ULN	50%	100%	No dose adjustment needed; discontinue if hepatitis
2 – 4 x ULN	25%	Caution	
> 4 x ULN	OMIT	Caution	

*Also consider dose modification for vincristine for severe increase in transaminases.

Renal Impairment

Creatinine Clearance (mL/min)	Vincristine (% previous dose)	Cyclophosphamide (% previous dose)	Rituximab
>50	No dose adjustment required.	100%	No dose adjustment required
10-50		May consider 75%	
< 10		50%; use with caution and monitor closely	

Dosage in the Elderly

No dose adjustment required. Exercise caution as older patients are more likely to experience serious adverse events (including cardiac, pulmonary, neurotoxicity or other grade 3/4 toxicity).

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F - Adverse Effects

Refer to riTUXimab, riTUXimab (SC), vinCRIStine, cyclophosphamide drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Infusion or hypersensitivity reactions (may be severe; with rituximab IV)	• Constipation • Administration-related reactions, including cutaneous (with rituximab subcut) • Alopecia	• Fatigue • Nausea, vomiting • Peripheral neuropathy (may be severe) • Headache • Rash (may be severe) • Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe) • Flu-like symptoms • Steroid effects (weight gain, GI irritation, hyperglycemia, insomnia, mood changes, myopathy, cataracts)	• Arterial/venous thromboembolism • Arrhythmia, ↑ QTc • Cardiotoxicity • GI obstruction/ perforation • Hepatotoxicity • Veno-occlusive disease • Pancreatitis • Pneumonitis • RPLS / PRES, PML • Optic and cranial nerve disorder • Autonomic neuropathy • Tumour lysis syndrome • SIADH • Nephrotoxicity • Cystitis • Bladder fibrosis • Vasculitis • Hemolysis • Hyperviscosity • Secondary malignancy • Hand-foot syndrome

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G - Interactions

Refer to riTUXimab, riTUXimab (SC), vinCRIStine, cyclophosphamide drug monograph(s) for additional details

- Consider withholding antihypertensive medication 12 hours prior to and during rituximab administration.
- Avoid combination of vincristine and verapamil or nifedipine; monitor closely if given concurrently.
- Avoid concurrent alcohol use with cyclophosphamide; may ↑ cyclophosphamide-induced nausea and vomiting; reduced anti-tumour activity has been observed in animal studies.
- Caution with use of CYP3A4 inhibitors and cyclophosphamide; avoid grapefruit for 48 hours before and on day of cyclophosphamide.
- Monitor serum phenytoin levels when used with vincristine, and adjust phenytoin dose as needed.

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H - Drug Administration and Special Precautions

Refer to riTUXimab, riTUXimab (SC), vinCRIStine, cyclophosphamide drug monograph(s) for additional details

Note: Different rituximab products are NOT INTERCHANGEABLE.

Administration

Rituximab IV and subcutaneous formulations are not interchangeable. The dosing and concentrations of these products are different.
Refer to Safety Considerations for the Implementation of Subcutaneous Rituximab Formulation

Rituximab should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.

riTUXimab (IV)

- DO NOT administer as an IV push or bolus.

- Dilute to a final concentration of 1-4 mg/mL in normal saline or D5W.
- To avoid foaming, gently invert the bag to mix the solution.
- Do not admix with other drugs.
- Administer rituximab through a dedicated line.
- Compatible with PVC or polyethylene bags.

Infusion rates:

First infusion:

- Recommended to be administered over a graduated rate: initial rate of 50 mg/h, then escalate rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h (about 4.25 hours in total).

Subsequent infusions:

- If no severe infusion reaction (grade 3 or 4) occurred with the first cycle, a rapid infusion of IV rituximab over a total of 90 minutes can be initiated with cycle 2 (20% of the dose in the first 30 min then the remaining 80% over 60 min).

- OR initial rate of 100 mg/h, then escalate rate in 100 mg/h increments every 30 minutes, to a maximum of 400 mg/h as tolerated (about 3.25 hours in total).

- Alternatively, subcutaneous administration of rituximab can be considered starting with cycle 2.

When bulky disease present or WBC > 25-50 x 10^9/L, consider:

- A slower infusion rate, or
- Split dosing over days 1-2, or
- Delaying rituximab treatment until chemotherapy has reduced the lymphocyte count

riTUXimab (SC):

Refer to Safety Considerations for the Implementation of Subcutaneous Rituximab Formulation

- Rituximab SC must not be self-administered.
- Rituximab SC is given subcutaneously into the abdominal wall only. Do not give in areas where the skin is red, tender, hard, bruised, or where there are moles or scars.
- Non-Hodgkin's lymphoma: Give SC over approximately 5 minutes
- Observe for at least 15 minutes after administration.
- Cold compresses and topical steroids may be helpful for local cutaneous reactions.
- If there are other SC medications, they should be given at separate sites.
- Compatible with polypropylene or polycarbonate syringes.

vinCRIStine:

FOR INTRAVENOUS USE ONLY. Vincristine is lethal if given intrathecally. No successful antidotes have been described. **Syringes containing this product should be labelled "WARNING – FOR INTRAVENOUS USE ONLY. FATAL if given by other routes."**

- Direct IV push not recommended, due to risk of inadvertent intrathecal administration.
- For intermittent IV use, may mix in small volume minibag (ie. 50mL NS or D5W for adults).
- Infuse IV via gravity. Infusion pumps should not be used peripherally, since they deliver infusions at higher pressures and may continue to infuse when extravasation occurs.
- During the infusion, suggest nurse to remain present with the patient to observe the IV site for extravasation.

Cyclophosphamide:

- Oral hydration is strongly encouraged; poorly hydrated patients may need more IV hydration.
- Inadequate total hydration may result in dose-related hemorrhagic cystitis.
- Patients should be encouraged to empty their bladder frequently to minimize dwell times.
- Oral tablets should be administered as a single dose in the morning, with or without food.
- Morning administration of cyclophosphamide is recommended, to decrease the amount of drug dwelling in the bladder overnight.
- Patients should avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications:

- Patients who have a hypersensitivity to any of the drug(s) or any of its components, or known hypersensitivity and anaphylactic reactions to proteins of similar mouse or human origin, to Chinese Hamster Ovary (CHO) cell proteins, or to rituximab, cyclophosphamide, vincristine, prednisone and its components
- Patients who have or have had PML, have active and/or severe infections, active hepatitis B, or severely immunocompromised (e.g. AIDS patients with very low CD4 or CD8 counts).
- Avoid the use of live vaccines.
- Vincristine intrathecal administration is absolutely contraindicated.
- (vincristine) patients with the demyelinating form of Charcot-Marie-Tooth Syndrome, childhood polio or with hypersensitivity to vinca alkaloids.
- (doxorubicin) Patients with severe myocardial insufficiency, arrhythmias or history of cardiac disease or recent myocardial infarction
- (doxorubicin) Patients with previous treatment with maximum cumulative doses of doxorubicin, other anthracyclines or anthracenediones
- (cyclophosphamide) patients with urinary outflow obstruction

Precautions:

- Exercise caution in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients may have increased risk of infection following rituximab treatment.
- Prior to starting rituximab in HBV seropositive patients, consultation with a liver disease expert is recommended to determine ongoing monitoring of HBV reactivation and its management.
- Exercise caution in patients with neutrophil counts < 1.5 x 10^9/L and/or platelets < 75 x 10^9/L due to limited experience of rituximab in this patient group.
- Use rituximab with extreme caution in patients with pre-existing cardiovascular disease or in patients with high tumour burden. Consider steroids ± rituximab slow infusions or infusions split over 2 days for patients with bulky disease or > 25 x 10^9/L circulating malignant cells.
- Use rituximab with caution in patients with pulmonary insufficiency or lung tumour infiltration, and in patients with myelosuppression.
- Reduced immunogenicity may occur with use of inactivated vaccines.
- Use vincristine with caution with other neuromuscular disorders, neurotoxic/ototoxic drugs, in leukopenia, complicating infection, or and in patients with Guillain-Barre Syndrome.
- Vincristine should not be given to patients who are receiving radiation that includes liver portals.
- Use cyclophosphamide with caution in patients with adrenal insufficiency or when used in combination with neuromuscular blockers.

Pregnancy and Lactation:

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Effects on fertility: Yes

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Liver function tests; baseline and before each cycle
- Renal function tests; baseline and before each cycle
- Electrolytes, baseline and as clinically indicated
- Monitor patients during and for at least 15 minutes after each rituximab dose, longer in patients at higher risk of hypersensitivity reactions
- Clinical assessment of hypersensitivity/infusion reactions, local toxicity, tumour lysis syndrome, infection, bleeding, GI, pulmonary, skin, CNS, neurologic, cardiovascular and cystitis; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Monitor cardiovascular symptoms in patients who have cardiac conditions or recurrent cardiac events with rituximab; At each visit

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J - Administrative Information

Approximate Patient Visit	First cycle: 6 hours; subsequent cycles: 1 to 4 hours
Pharmacy Workload (average time per visit)	26.435 minutes
Nursing Workload (average time per visit)	74.833 minutes

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K - References

Hochster H, Weller E, Gascoyne RD, et al. Maintenance Rituximab After Cyclophosphamide, Vincristine, and Prednisone Prolongs Progression-Free Survival in Advanced Indolent Lymphoma: Results of the Randomized Phase III ECOG1496 Study. JCO 2009; 27: 1607-14.

Marcus R, Imrie, K, Solal-Celigny P, et al. Phase III Study of R-CVP Compared With Cyclophosphamide, Vincristine, and Prednisone Alone in Patients With Previously Untreated Advanced Follicular Lymphoma. JCO 2008: 26; 4579-86.

Marcus, R., et al., CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood, 2005. 105(4): p. 1417-23.

Salar A, Casao D, Cervera M, et al. Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. Eur J Haematol 2006: 77: 338–340

Sehn LH, Donaldson J, Filewich A, et al. Rapid Infusion Rituximab in Combination with Steroid Containing Chemotherapy Can Be Given Safely and Substantially Reduces Resource Utilization. Blood 2004; 104(11): A1407.

Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. Lancet Haematol. 2017 Jun;4(6):e272-e282.

PEBC Advice Documents or Guidelines

- Rituximab in Lymphoma and Chronic Lymphocytic Leukemia

November 2023 Modified Pregnancy/lactation section

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate

that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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