Regimen Monograph

A - Regimen Name

CHOP+R Regimen

Cyclophosphamide-Hydroxyldaunorubicin (DOXOrubicin)-ONCOVIN® (VinCRIStine)-Prednisone-riTUXimab

Disease Site

Hematologic
- Lymphoma - Non-Hodgkin's High Grade
- Lymphoma - Non-Hodgkin's Intermediate Grade

Intent

Curative
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

Therapy for previously untreated patients with agressive histology CD20-positive B-cell lymphomas (Diffuse Large B-Cell Lymphoma (DLBCL) or a variant of DLBCL such as mediastinal sclerosing B-cell lymphoma, T-cell–rich B-cell lymphoma, Burkitt-like lymphoma, or intravascular lymphoma), including previously untreated HIV-associated lymphomas (provided CD4 count ≥ 50 mm^3), who are candidates for curative treatment and have not previously received rituximab.

There is insufficient evidence for maintenance rituximab in aggressive histology B-cell lymphomas.

Supplementary Public Funding

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

riTUXimab (subcut)
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - Aggressive Histology Lymphoma)

riTUXimab (subcut)
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - HIV-Related Aggressive Histology B-cell Lymphoma)

riTUXimab
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - Aggressive Histology Lymphoma)

riTUXimab
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - HIV-Related Aggressive Histology 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	100 mg	PO daily	Days 1 to 5*

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

riTUXimab	375 mg /m²	IV	Day 1
vinCRIStine	1.4 mg /m²	IV (max 2 mg)	Day 1
DOXOrubicin	50 mg /m²	IV	Day 1
cyclophosphamide	750 mg /m²	IV	Day 1

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

Rituximab IV:

riTUXimab	375 mg /m²	IV	Day 1

OR

Rituximab (subcut):
The subcutaneous formulation must only be given at the second or subsequent cycles, if the patient has previously received at least one full rituximab IV dose.

riTUXimab (subcut)	1400 mg	Subcut	Day 1

Plus CHOP chemotherapy

prednisone	100 mg	PO daily	Days 1 to 5*

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

vinCRIStine	1.4 mg /m²	IV (max 2 mg)	Day 1
DOXOrubicin	50 mg /m²	IV	Day 1
cyclophosphamide	750 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a usual total of 6 to 8 cycles unless disease progression or unacceptable toxicity occurs.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Febrile Neutropenia Risk: Moderate

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

Hematologic and Non-Hematologic Toxicities:

Toxicity	Doxorubicin[1] (% previous dose)	Vincristine[1] (% previous dose)	Cyclophosphamide[1] (% previous dose)	Rituximab IV or Subcut[1,2] (% previous dose)
Grade 4 hematological, febrile neutropenia, bleeding	75%, or G-CSF for low ANC	100%	75%, or G-CSF for low ANC	100%

Grade 3 non-hematological toxicity	75%	100%	75%	100% or delay
Neurotoxicity	100%	***Mild***: 67%; ***Moderate***: Hold until recovery, then ↓ 50%; ***Severe***: Discontinue	100%	100%
Cystitis	100%	100%	Hold until resolution	100%
Grade 4 organ toxicity	Discontinue	Discontinue	Discontinue	Discontinue
• Severe mucocutaneous toxicity • Serious/life-threatening cardio-pulmonary events • PML/RPLS • Reactivation of TB or hepatitis B • Evidence of active hepatitis	Discontinue	Discontinue	Discontinue	Discontinue

[1]Prior to retreatment, major organ toxicity should have recovered to ≤ grade 2 and 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.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms.	• 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.

	Restart: • Once symptoms have resolved, restart at 50% of the IV rate at which the IR occurred.	
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

Consider dose modification for **doxorubicin** and **vincristine** for severe increase in transaminases.

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

Renal Impairment

Creatinine Clearance (mL/min)	**Doxorubicin (% previous dose)**	**Vincristine (% previous dose)**	**Cyclophosphamide (% previous dose)**	**Rituximab**
>50	No dose adjustment required	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 (subcut), vinCRIStine, DOXOrubicin, 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 and hypersensitivity reactions (may be severe; with IV rituximab) • Alopecia • Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe)	• Nausea, vomiting • Peripheral neuropathy (may be severe) • Administration-related reactions, including cutaneous (with rituximab subcut) • Mucositis	• Fatigue • Headache, flu-like symptoms • Rash (may be severe) • Diarrhea • Constipation • Steroid effects (weight gain, GI irritation, hyperglycemia, insomnia, mood changes, myopathy, cataracts)	• Arterial / venous thromboembolism • Arrhythmia, prolonged QTc • Cardiotoxicity • GI obstruction / perforation • Hepatotoxicity • Veno-occlusive disease • Pancreatitis • Pneumonitis • Nephrotoxicity • Cystitis • Bladder fibrosis • Tumour lysis syndrome • SIADH • Optic and cranial nerve disorder • Autonomic neuropathy • PML, PRES/ RPLS • Hemolysis

			• Vasculitis • Hyperviscosity • Secondary malignancies • Radiation recall reaction • Photosensitivity • Infertility

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G - Interactions

Refer to riTUXimab, riTUXimab (subcut), vinCRIStine, DOXOrubicin, cyclophosphamide drug monograph(s) for additional details.

- Consider withholding antihypertensive medication 12 hours prior to and during rituximab administration.
- Avoid using stavudine or zidovudine with doxorubicin
- Avoid use of calcium channel blockers (e.g. verapamil) or bevacizumab with doxorubicin due to cardiotoxicity
- Avoid anthracycline-based therapy for up to 28 weeks after stopping trastuzumab
- Avoid concurrent alcohol use with cyclophosphamide; may ↑ cyclophosphamide-induced nausea and vomiting; reduced anti-tumour activity has been observed in animal studies
- Monitor serum digoxin levels when used with doxorubicin; levels may decrease
- Caution with use of CYP3A4 inhibitors and cyclophosphamide; avoid grapefruit for 48 hours before and on day of cyclophosphamide
- Avoid combination of vincristine and verapamil or nifedipine; monitor closely if given concurrently
- Monitor serum phenytoin levels when used with doxorubicin or vincristine, and adjust phenytoin dose as needed

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H - Drug Administration and Special Precautions

Refer to riTUXimab, riTUXimab (subcut), vinCRIStine, DOXOrubicin, 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 (Subcut):

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 (i.e. 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.

DOXOrubicin:

- Slow push through sidearm of free flowing IV (5% Dextrose or Normal Saline). Depending on the dose volume and vein condition, administer the dose between 3 to 10 minutes to minimize thrombosis risk or extravasation.
- Do not admix with other drugs unless data are available; precipitates with fluorouracil and heparin.
- Avoid contact with alkaline solutions as this can lead to hydrolysis of doxorubicin
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly as per local guidelines.

Cyclophosphamide:

- Oral hydration is strongly encouraged; for IV cyclophosphamide: 2-3 L of fluid/day; 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.
- Morning administration of cyclophosphamide is recommended, to decrease the amount of drug dwelling in the bladder overnight.
- Infuse in 250 mL sodium chloride 0.9% over 30 minutes.
- For IV infusion, may reconstitute cyclophosphamide with sodium chloride 0.9% or sterile water for injection before further dilution.
- Do not reconstitute or dilute with benzyl alcohol-containing solutions (i.e. Bacteriostatic sodium chloride), since it may catalyse the decomposition of cyclophosphamide
- Avoid the use of aluminum-containing preparation and administration equipment, since darkening of aluminum and gas production have been reported.

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, other anthracyclines or anthracenediones (i.e. epirubicin, daunorubicin, mitoxantrone or mitomycin C), or known hypersensitivity and anaphylactic reactions to proteins of similar mouse or human origin, to Chinese Hamster Ovary (CHO) cell proteins
- 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

Warning/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 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/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 functions tests; baseline and before each cycle
- Electrolytes; baseline and as clinically indicated
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors (including prior therapy with epirubicin, mitoxantrone, trastuzumab or other cardiotoxic drug) and cumulative doxorubicin doses > 450mg/m^2; 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, tumour lysis syndrome,

infection, bleeding, GI, pulmonary, skin, CNS, cardiovascular effects, neurotoxicity and cystitis; at each visit

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

Suggested Clinical Monitoring

- Monitor closely for cardiovascular symptoms for patients who have cardiac conditions or recurrent cardiac events with rituximab

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J - Administrative Information

Approximate Patient Visit	First cycle: 6 hours; subsequent cycles: 2 to 5 hours
Pharmacy Workload (average time per visit)	46.499 minutes
Nursing Workload (average time per visit)	89.833 minutes

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K - References

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Lugtenburg P, Avivi I, Berenschot H et al. Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study. Haematologica. 2017;102(11):1913-1922.

Rummel M, Kim TM, Aversa F et al. Preference for subcutaneous or intravenous administration of rituximab among patients with untreated CD20+ diffuse large B-cell lymphoma or follicular lymphoma: results from a prospective, randomized, open-label, crossover study (PrefMab). Ann Oncol. 2017;28(4):836-842.

PEBC Advice Documents or Guidelines

- Rituximab in Lymphoma and Chronic Lymphocytic Leukemia

November 2023 Modified Administration, Pregnancy/breastfeeding, and Monitoring sections

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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.

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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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