Regimen Monograph

A - Regimen Name

CHOP+R Regimen

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

Disease Site	Hematologic - Lymphoma - Non-Hodgkin's High 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 or relapsed/refractory patients with agressive histology CD20-positive B-cell lymphomas, 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) **riTUXimab** New Drug Funding Program (Rituximab - HIV-Related, Aggressive Histology,

B-cell Lymphoma) (NDFP Website)

riTUXimab
New Drug Funding Program (Rituximab - Aggressive Histology Lymphoma) (NDFP Website)

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B - Drug Regimen

prednisone	100 mg	PO daily	Days 1 to 5*

*On Day 1 to be given as part of pre-medication before Rituximab (Outpatient prescription in multiples of 50mg tablets)

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

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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 Summary

Rituximab premedication:

• Acetaminophen 650mg PO

• Diphenhydramine 50mg PO/IV

• If high volume disease, consider steroids and prophylaxis for tumour lysis

HBsAg positive patients should receive antiviral prophylaxis during and after rituximab. HBsAg negative, but HBcAb positive patients should be considered for antiviral prophylaxis and be closely monitored for viral reactivation by a HBV expert.

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E - Dose Modifications

Screen patients for hepatitis B prior to starting treatment. 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. The following recommendations are in use at some centres.

Dosage with toxicity

Hematologic and Non-Hematologic Toxicities: See Appendix 6 for general recommendations.

Toxicity	Doxorubicin[1] (% previous dose)	Vincristine[1] (% previous dose)	Cyclophosphamide[1] (% previous dose)	Rituximab[1,2] (% previous dose)
Grade 4 hematological ≥ 7 days, 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
Grade 4 organ toxicity	Discontinue	Discontinue	Discontinue	Discontinue
Neurotoxicity	100%	***Mild***: 67%; ***Moderate***: Hold until	100%	100%

		recovery, then ↓ 50%; ***Severe**:* Discontinue		
Toxicity	**Doxorubicin**	**Vincristine**	**Cyclophosphamide**	**Rituximab**
• Severe rash • Serious/life-threatening cardio-pulmonary events • PML/RPLS; Reactivation of TB or hepatitis B • Evidence of active hepatitis	Discontinue	Discontinue	Discontinue	Discontinue
Grade 1-2 infusion related	--	--	--	Stop or slow infusion; exclude respiratory symptoms; treat symptomatically. Re-start at 50% previous rate after resolution of symptoms.
≥Grade 3 infusion-related/pulmonary	--	--	--	Discontinue; Manage appropriately; monitor patient until complete resolution.

[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

Hepatic Impairment

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

Bilirubin	**Doxorubicin (% previous**	**Vincristine**	**Cyclophosphamide**	**Rituximab**

	dose)	(% previous dose)	(% previous dose)	
1 – 2 X ULN	50%	50%	100%	No adjustment required
2 – 4 x ULN	25%	25%	Caution	No adjustment required
> 4 ULN	OMIT	OMIT	Caution	No adjustment required

Renal Impairment

Creatinine Clearance (mL/min)	Doxorubicin (% previous dose)	Vincristine (% previous dose)	Cyclophosphamide (% previous dose)	Rituximab
30-50	No dose adjustment required.	No dose adjustment required.	100%	No adjustment required.
10-30			50-75%	
< 10			50% or Omit	

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F - Adverse Effects

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

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Hypersensitivity reactions (may be severe) • Myelosuppression ± bleeding, infection (may be severe, includes opportunistic) • Alopecia • Nausea and vomiting • ↑ LFTs • Fatigue • Immunosuppression ± viral / TB	• SIADH • Arrhythmia, cardiotoxicity • Pancreatitis • Tumour lysis syndrome • Nephrotoxicity, hemolytic uremic syndrome • Photosensitivity • PML • Arterial/venous thromboembolism • GI obstruction/perforation

reactivation • Anorexia • Constipation, diarrhea • Headache • Mucositis • Peripheral neuropathy (may be severe) • Rash (may be severe) • Flu-like symptoms • Steroid effects (weight gain, hyperglycemia, gastric irritation, insomnia, mood changes)	• Pneumonitis • RPLS • Hemolysis • Secondary malignancies • Vasculitis • Steroid effects (myopathy, cataracts, osteoporosis)

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

Rituximab:

- First infusion: initial rate of 50 mg/h, then escalate rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h.
- If first infusion well-tolerated, start subsequent infusions at 100 mg/hr, then escalate rate in 100 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr as tolerated
- Published data suggest that a 90 minute infusion (20% of the dose in the first 30 min then the remaining 80% over 60 min) can be used for second and subsequent infusions if no reaction occurred with the 1st infusion.
- Consider a slower infusion rate for patients with high bulk disease who are at a higher risk of tumor lysis syndrome and infusion related reactions.

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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.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- LFTs; baseline and before each cycle
- Renal function tests; baseline and before each cycle
- The Hematology Disease Site group recommends screening patients for hepatitis B surface antigen (HBsAg) and core antibody (HBcAb) prior to starting treatment with rituximab. If seropositive, consult with an expert in HBV and monitor closely.
- Clinical toxicity assessment of hypersensitivity reactions, tumour lysis syndrome, infection, bleeding, GI, pulmonary, skin or CNS toxicity, cardiotoxicity, neurotoxicity, hypotension and cystitis; at each visit
- Baseline and regular cardiac examination for patients with cardiac risk factors (including prior therapy with epirubicin, mitoxantrone, or other cardiotoxic drug) and cumulative doxorubicin doses > 450mg/m^2.
- 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	4 to 7 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

Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-42.

Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. J Clin Oncol 2005;23(18):4117-26.

Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24(19):3121-7.

Rituximab drug monograph, Cancer Care Ontario.

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: 338–40.

Sehn LH, Donaldson J, Filewich A, et al. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. Blood 2007;109(10):4171-3.

PEBC Advice Documents or Guidelines

- Rituximab in Lymphoma and Chronic Lymphocytic Leukemia

October 2017 Replaced regimen category with evidence-informed

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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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