Regimen Monograph

A - Regimen Name

GDP+RITU Regimen

Gemcitabine-Dexamethasone-PLATINOL® (CISplatin)-Rituximab

Disease Site

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

Intent

Curative

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 relapsed aggressive histology CD20+ lymphoma with intent to proceed to autologous stem cell transplantation, in patients previously treated with rituximab-based chemoimmunotherapy (e.g., R-CHOP) for aggressive histology lymphoma and had a best response of at least partial response

Supplementary Public Funding

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

dexamethasone
ODB - General Benefit (dexamethasone) (ODB Formulary)

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

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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.

dexamethasone*	40 mg	PO	Days 1 to 4

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

riTUXimab	375 mg /m²	IV	Day 1
gemcitabine	1000 mg /m²	IV	Days 1 and 8
CISplatin	75 mg /m²	IV	Day 1

Cycle 2 and onwards [total of 2 to 3 cycles (refer to Cycle Frequency section), 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, and only after at least one full rituximab IV dose.

riTUXimab (subcut)	1400 mg	Subcut	Day 1

Plus GDP chemotherapy:

dexamethasone*	40 mg	PO	Days 1 to 4

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

gemcitabine	1000 mg /m²	IV	Days 1 and 8
CISplatin	75 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

- If complete or partial response occurs after 2 cycles, may proceed to autologous stem cell transplant (ASCT). May receive a third cycle if patient has not achieved a complete or partial response after 2 cycles*.

*rituximab (IV and subcut combined) funded by NDFP for up to 3 cycles

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D - Premedication and Supportive Measures

Antiemetic Regimen: High (Day 1)
Low (Day 8)

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.
- The day 1 dexamethasone dose can be given IV before chemotherapy to prevent emesis and infusion reactions.
- Consider use of filgrastim to maintain dose intensity for patients at high risk of febrile

neutropenia or prolonged neutropenia.

- Standard regimens for Cisplatin premedication and hydration should be followed. Refer to local guidelines.

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 dexamethasone 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

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from the LY.12 study (Crump *et al,* 2014).

See premedication and monitoring sections for rituximab supportive care, screening and monitoring recommendations.

Dosage with toxicity

Dose adjustments are to be made based on the system showing the greatest degree of toxicity. Doses held during a cycle of therapy do not need to be made up. All doses should go back to 100% of the planned dose for the next cycle, unless otherwise indicated below.

Table 1: Dosage with Hematologic Toxicities

Day(s) of Cycle	Absolute Neutrophil Count (ANC) ($x10^9$/L)		Platelets ($x10^9$/L)	Action This Cycle
Day 1	≥ 1	AND	≥ 75	Give 100% dose of all drugs
	≥ 1	AND	< 75	Delay 1 week* If platelets then ≥ 75, give 100% dose of all drugs.

				If platelets still < 75 but ≥ 50, give 100% dose rather than delay further; support with platelet transfusions as necessary.
	< 1	AND	≥ 75	Delay 1 week* If ANC then ≥ 1, give 100% of all drugs. If ANC still < 1 but ≥ 0.5, give 100% dose rather than delay further; initiate GCSF. **
	< 1	AND	< 75	Delay 1 week* • If ANC at that point ≥ 0.5 and platelets ≥ 50: give 100% of all drugs; initiate GCSF; support with platelet transfusions. OR • If ANC at that point < 0.5 and/ or platelets < 50: defer and check counts every 3-4 days. When both ANC ≥ 0.5 and platelets ≥ 50, resume as described above.
Day 8	≥ 1	AND	≥ 75	Give 100% dose of gemcitabine
	≥ 0.5 and < 1	AND	≥ 75	Give 100% dose gemcitabine and initiate GCSF* OR 75% of day 1 dose
	----		< 75 and ≥ 50	75% of day 1 dose
	< 0.5	OR	< 50	Omit gemcitabine dose this cycle and initiate GCSF **
* If counts presumed to be low due to marrow involvement, treat after 1 week delay (i.e. at 4 weeks or Day 28) despite counts. ** GCSF should be given prophylactically for all future cycles				

Table 2: Dosage with Non-Hematologic Toxicities

Serum creatinine must be ≤ 1.5 X ULN and bilirubin ≤ 1.5 X ULN prior to treatment at full dose. Refer to table below for dosing with elevated creatinine or bilirubin

If the toxicity is believed to be due to dexamethasone, then discontinue dexamethasone for that cycle and re-assess for future cycles.

Day(s) of Cycle	Worst grade in previous period		Gemcitabine	Cisplatin	Rituximab IV	Rituximab Subcut
Day 1	≥ Grade 2 pneumonitis		Hold; if confirmed, discontinue causal agent			
	Grade 3 other toxicity*		75%	75%	Discontinue	Discontinue
	Creatinine	1.5 – 3 x ULN	100%	75% (for this and all future cycles)	100% but monitor carefully	100% but monitor carefully
		> 3 x ULN	Hold for one week; if recovers to ≤ 3 x ULN modify dose as above. If not, discontinue			
	Bilirubin	1.5 – 3 x ULN	75% (for this and all future cycles)	100%	100%	100%
		> 3 x ULN	Hold for one week; if recovers to ≤ 3 x ULN modify dose as above. If not, discontinue		100%; discontinue if hepatitis	100%; discontinue if hepatitis
	Grade 4 other organ toxicity		Hold one week. If toxicity does not resolve to level acceptable for dose reduction (see above), discontinue treatment.		Discontinue	Discontinue
Day 8	≤ Grade 2		100%	n/a	n/a	n/a
	≥ Grade 2 pneumonitis		Hold, if confirmed, discontinue	n/a	n/a	n/a
	Grade 3 other toxicity **		75% of day 1 dose	n/a	n/a	n/a
	Grade 4		Hold	n/a	n/a	n/a

Day 1 or 8	• Severe mucocutaneous toxicity • Serious/life-threatening cardio-pulmonary events • Reactivation of tuberculosis or hepatitis B • Evidence of active hepatitis • PML / PRES • Hemolytic Uremic Syndrome (HUS) • Capillary Leak Syndrome (CLS) • Posterior reversible encephalopathy syndrome (PRES)	Discontinue
* Except nausea, vomiting, and alopecia; In the event of grade 3 tinnitus, reduce cisplatin dose only. ** Patient may receive a dose reduction or discontinue treatment. This decision will depend upon the type of non-hematologic toxicity seen and is at the discretion of the treating physician.		

Management of 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

See Table 2 above

Renal Impairment

See Table 2 above

Dosage based on gender:

Gemcitabine clearance is lower in women but no dose adjustment is necessary.

Dosage in the Elderly

Exercise caution as geriatric patients may be at higher risk of developing nephrotoxicity,

ototoxicity/neurotoxicity or hematologic adverse effects with cisplatin and serious adverse events (including cardiac, pulmonary, or other grade 3/4 toxicity) with rituximab. Gemcitabine clearance is lower in the elderly but no dose adjustment necessary.

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F - Adverse Effects

Refer to riTUXimab, riTUXimab (SC), gemcitabine, CISplatin 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; especially with rituximab IV) • Nausea, vomiting (may be severe) • ↑ LFTs	• Fatigue • Ototoxicity (may be severe) • Nephrotoxicity (may be severe) • Neurotoxicity (may be severe) • Electrolyte abnormalities • Rash (may be severe) • Flu-like symptoms • Proteinuria • Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe) • Administration-related reactions, including cutaneous (with rituximab subcut)	• Headache • Musculoskeletal pain • Alopecia • Diarrhea • Edema • Steroid effects (weight gain, GI irritation, hyperglycemia, insomnia, mood changes, myopathy, cataracts)	• Arrhythmia • Cardiotoxicity • Arterial/venous thromboembolism • GI obstruction/ perforation • Pneumonitis, ARDS • RPLS / PRES, PML • Seizures • Optic and cranial nerve disorder • Tumour lysis syndrome • Capillary leak syndrome • SIADH • Vasculitis, thrombotic microangiopathy • Raynaud's • Hemolysis, hemolytic uremic syndrome • Hyperviscosity • Secondary malignancy

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G - Interactions

Refer to riTUXimab, riTUXimab (subcut), gemcitabine, CISplatin drug monograph(s) for additional details

- Avoid nephrotoxic and ototoxic drugs (i.e. aminoglycosides) due to additive effects.
- Concomitant use of renally excreted drugs (i.e. methotrexate) may decrease renal clearance and enhance toxicities of these drugs. Avoid use, if possible. If not possible, modify doses as necessary.
- Cisplatin may decrease phenytoin levels; monitor levels and patient.
- Gemcitabine may increase INR and bleeding risk in patients taking warfarin; monitor closely and adjust INR as needed
- Antihypertensive agents may potentiate infusion-related hypotension with rituximab; consider withholding 12 hours before and during administration

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H - Drug Administration and Special Precautions

Refer to riTUXimab, riTUXimab (subcut), gemcitabine, CISplatin 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 (subcut) must not be self-administered.
- Rituximab (subcut) 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.
- Give subcutaneously 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 subcutaneous medications, they should be given at separate sites.
- Compatible with polypropylene or polycarbonate syringes.

Gemcitabine:

- Dilute reconstituted drug in normal saline for IV infusion; to a minimum final concentration of 0.1 mg/mL.
- Infuse over 30 minutes through free-flowing IV.

Cisplatin:

- Cisplatin was given IV over 1 hour in the LY.12 clinical trial.
- Ensure good urinary output during chemotherapy visit. Patient should void at least once during chemotherapy visit. Use locally approved hydration regimens.
- Additional hydration may be ordered for hypovolemic patients.
- Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at discretion of physician.
- Adequate hydration and urinary output must be maintained for 24 hours following cisplatin treatment.
- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.
- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.

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

Contraindications

- Patients with known hypersensitivity and anaphylactic reactions to proteins of similar mouse or human origin, to Chinese Hamster Ovary (CHO) cell proteins or to any component of rituximab, platinum-containing compounds, dexamethasone or gemcitabine.
- 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
- Patients with pre-existing renal impairment and hearing impairment, unless the possible benefits of treatment outweigh the risks with cisplatin

Other Warnings/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 with gemcitabine in patients with compromised bone marrow; limited experience with rituximab in patients with neutrophil counts < 1.5 x 10^9/L and/or platelets < 75 x 10^9/L
- Use rituximab with extreme caution in patients with pre-existing cardiovascular disease or in patients with high tumour burden. Consider additional steroids ± 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 the use of inactivated vaccines.
- All patients should receive appropriate hydration and antiemetic protocols according to local guidelines.
- Gemcitabine use in patients with impaired hepatic function, including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis may lead to exacerbation of the hepatic insufficiency
- Use gemcitabine with caution in patients with renal impairment

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).

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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

- Audiogram; Baseline and as clinically indicated
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium.; Baseline and before each cycle
- CBC; Baseline and before each visit
- LFTs; baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- Monitor patient 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 (including flu-like symptoms), local reactions, tumour lysis syndrome, infection, bleeding, hemolysis, fatigue, GI (including nausea/vomiting), ototoxicity, pulmonary, skin, CNS/neurotoxicity, cardiovascular side effects; 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 rituximab visit
- INR for patient receiving warfarin; Baseline and as clinically indicated
- Urinalysis; Baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	Day 1: Up to 8 hours (first cycle); 3.5-7 hours (subsequent cycles); Day 8: 0.75 hour
Pharmacy Workload (average time per visit)	38.371 minutes
Nursing Workload (average time per visit)	62.917 minutes

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K - References

Cisplatin, gemcitabine and rituximab drug monographs, Cancer Care Ontario.

Crump M, Baetz T, Couban S, et al. Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology b-cell non-Hodgkin lymphoma. Cancer 2004;101(8):1835-42.

Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 2014 Nov 1;32(31):3490-6.

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

January 2024 Modified Drug regimen and Drug administration 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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