BC Cancer Protocol Summary for Treatment of Lymphoma with Gemcitabine, Dexamethasone and Platinum

Protocol Code	*LYGDP*
Tumour Group	*Lymphoma*
Contact Physician	*Dr Laurie Sehn*

ELIGIBILITY:

- Greater than or equal to 18 years of age
- Aggressive histology lymphoma in the WHO classification including
  - diffuse large B-cell lymphoma
  - mediastinal large B-cell lymphoma
  - T-cell rich B-cell lymphoma
  - intravascular large B-cell lymphoma
- Relapsed disease
- ECOG Performance Status 0,1,2 or 3
- No major impairment of renal, hepatic, or bone marrow function

TESTS:

- Baseline, then as indicated:
  - Required before first treatment: CBC & diff, creatinine, total bilirubin, ALT
  - Required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2: HBsAg, HBsAb, HBcoreAb
  - Recommended but optional: total bilirubin, alkaline phosphatase, magnesium, calcium
- Before each treatment:
  - Day 1: CBC & diff, creatinine
  - Day 8: CBC & diff
    Creatinine (if cisplatin dose is given day 1 and 8)
- Before each treatment cycle: use calculated creatinine clearance and serum creatinine to determine CISplatin dose, see dose modifications below.
- If clinically indicated: HBV viral load, ALT (see protocol SCHBV)

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

SUPPORTIVE MEDICATIONS:

High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.

TREATMENT:

Drug	Dose†	BC Cancer Administration Guideline
gemcitabine	1000 mg/m^2 day 1 & 8	IV in 250 mL NS over 30 min*
dexamethasone	40 mg/d days 1 to 4	PO daily in the morning *(Note: The anti-emetic premedication is separate from the Dexamethasone given as part of the protocol; both should be prescribed separately.)*
CISplatin¥	75 mg/m^2 day 1	Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g MgSO4, 30 g mannitol over 1 hour

† Consider dose reduction to 75% for gemcitabine and cisplatin or carboplatin in patients greater than 70 years of age

* gemcitabine may be given during prehydration for CISplatin

¥ Alternatively carboplatin may be used instead of cisplatin. See Renal Dysfunction under Dose Modifications. Note: it is acceptable for physicians to substitute CARBOplatin for CISplatin for reasons other than reduced GFR (for example, concerns around ototoxicity with CISplatin).

Estimate calculated creatinine clearance (CrCl) with following formula:

$$\text{CrCl (mL/min)} = \frac{\text{N x (140-age in years) x wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

(N=1.04 for females, N=1.23 for males)

Borderline cases (CrCl 60 to 70 mL/min): perform nuclear renogram for GFR, if available

Repeat every 21 days. Maximum prior to high dose chemotherapy and stem cell transplant, 3 cycles; otherwise 6 cycles. Discontinue if definite progression at any time. A Compassionate Access Program approval is required to continue beyond 6 cycles.

DOSE MODIFICATIONS:

1. **Hematological on Day 1**

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (all drugs)
greater than or equal to 1.0	and	greater than or equal to 75	100%
greater than or equal to 1.0	and	less than 75	Delay 1 week*
			If platelets greater than or equal to 75 give 100% dose of all drugs If platelets less than 75 but greater than 50, proceed at 100% and support with platelet transfusions
less than 1.0	and	greater than or equal to 75	Delay 1 week*
			If ANC greater than or equal to 1 give 100% If ANC less than 1 but greater than or equal to 0.5, proceed at 100% and start filgrastim**
less than 1.0	and	less than 75	Delay 1 week*
			If ANC greater than or equal to 0.5 and platelets greater than or equal to 50, proceed with 100% and start filgrastim with platelet transfusions If ANC less than 0.5 and/or platelets less than 50, defer and check counts every 7 days. When both ANC greater than or equal to 0.5 and platelets greater than or equal to 50, resume as above

*if counts presumed to be low due to marrow involvement, treat after 1 week delay (i.e at 4 weeks) despite counts

** filgrastim should be given prophylactically for all future cycles.

Hematological on Day 8:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose (all drugs)
greater than or equal to 1.0	and	greater than or equal to 75	100%
greater than or equal to 0.5 and less than 1.0	and	greater than or equal to 75	100% gemcitabine (and cisplatin) and start filgrastim* OR Reduce gemcitabine (and cisplatin) dose to 75% of current cycle's day 1 dose
greater than or equal to 1.0	and	less than 75 and greater than or equal to 50	Reduce gemcitabine (and cisplatin) dose to 75% of current cycle's day 1 dose
greater than or equal to 0.5 and less than 1.0	and	less than 75 and greater than or equal to 50	Reduce gemcitabine (and cisplatin) to 75% of current cycle's day 1 dose
less than 0.5	or	less than 50	Omit gemcitabine (and cisplatin) and start filgrastim**

*if counts presumed to be low due to marrow involvement, treat after 1 week delay (i.e at 4 weeks) despite counts

** filgrastim should be given prophylactically for all future cycles

2. **Renal Dysfunction**

Delay for one week if *serum* creatinine greater than 3 x ULN where ULN = local upper limit of normal range. If serum creatinine less than 3 x ULN adjust CISplatin dose as follows

Creatinine clearance (ml/minute)	CISplatin dose	Gemcitabine dose
greater than or equal to 60	75 mg/m^2 on Day 1	100%
45 to 59	37.5 mg/m^2 on Days 1 and 8 or go to CARBOplatin¥ option	100%
less than 45	***Delay*** (or use CARBOplatin¥ option)	***Delay/Omit**** (or 100% if CARBOplatin¥ option)

Delay if day 1; if day 8, omit if serum creatinine greater than 3 x ULN where ULN = local upper limit of normal range.

¥Alternatively CARBOplatin can be used instead of CISplatin per physician discretion for reasons other than reduced GFR (for example, concerns around ototoxicity).

Drug	Dose	BC Cancer Administration Guideline
CARBOplatin	AUC 5 on Day 1 only Dose= AUC x (GFR+25) (maximum 800 mg)	IV in 100 to 250 mL NS over 30 minutes

The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR. When a nuclear renogram is available, this clearance would take precedence. Maximum carboplatin dose is 800 mg.

Note: The same method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

Consider re-calculation of CARBOplatin dose if serum creatinine changes ± 20% from baseline.

Prehydration is not needed if CARBOplatin is given.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Thrombocytopenia**: Support with platelet transfusion may be required.
3. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
4. **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
5. **Hepatitis B Reactivation**: See SCHBV protocol for more details.

Call Dr. Laurie Sehn or tumor group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Crump 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. JCO 2014; 32(31):3490-96.
2.Gopal et al. Efficacy and safety of gemcitabine, carboplatin, dexamethasone, and rituximab in patients with relapsed/refractory lymphoma: a prospective multi-center phase II study by the Puget Sound Oncology Consortium. Leuk Lymphoma. 2010; 51(8):1523-9.
3. Moccia et al. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma. Leuk Lymphoma. 2017; 58(2):324-332.