

BC Cancer Protocol Summary for Treatment of Recurrent and Refractory Neuroblastoma, Ewing's Sarcoma, Osteogenic Sarcoma or Rhabdomyosarcoma with Topotecan and Cyclophosphamide

Protocol Code SAAVTC

Tumour Group Sarcoma

Contact Physician Dr. Christine Simmons

ELIGIBILITY:

- Relapsed/refractory Ewing's sarcoma, rhabdomyosarcoma, intra-abdominal small round blue cell tumour, or neuroblastoma
- ECOG PS 0-2
- Adequate hematologic parameters (ANC greater than or equal to $1.5 \times 10^9/L$, and platelets greater than or equal to $100 \times 10^9 /L$).
- Adequate hepatic and renal function

EXCLUSIONS:

- Creatinine clearance less than 40 mL/min. Use with caution in patients with renal dysfunction. See DOSE MODIFICATIONS for reduction in dose in patients with renal dysfunction.
- ECOG PS 3-4

TESTS:

- Baseline: CBC & diff, platelets, creatinine, BUN, bilirubin, ALT, sodium, potassium, phosphate, albumin, urinalysis (r+m)
- Before each treatment cycle (Day 1):
 - CBC & diff, platelets, creatinine, BUN, bilirubin, ALT, sodium, potassium, phosphate, albumin
 - Urinalysis (r+m). Notify physician if patient has hematuria.
- Weekly: CBC & diff, platelets

PREMEDICATIONS:

- ondansetron 8 mg PO prior to treatment
- dexamethasone 8 mg PO/IV prior to treatment
- prochlorperazine 10 mg PO prn
- LORazepam 1 mg PO prn

PREHYDRATION:

- Ensure patient has taken at least 500 mL of fluid prior to each day of therapy; if not, prehydrate daily with NS 500 mL over 30 minutes to 1 hour.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
cyclophosphamide	250 mg/m ² /day x 5 days (days 1 to 5)	IV in 100 mL NS over 20 min to 1 hour
Administer topotecan after cyclophosphamide		
topotecan	0.5 mg/m ² /day x 5 days (days 1 to 5) OR If filgrastim support available: 0.75 mg/m ² /day x 5 days (days 1 to 5); please see note below	IV in 25 to 50 mL NS over 30 min IV in 50 mL NS over 30 min

- Repeat 5-day treatment every 21 days x 4 cycles

Posthydration:

- D5-NS at 500 mL over 30 minutes to 1 hour on days 1 to 4 or 5
- Instruct patient to drink 2 L of fluid over 24 hours

DOSE MODIFICATIONS:**1. Hematological:**

a) on treatment day:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (both drugs)
greater than or equal to 1.5	and	greater than or equal to 100	treat as per nadir
less than 1.5	or	less than 100	delay until recovery

b) at nadir:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (both drugs)
less than 0.5	or	less than 50	20% dose reduction

2. **Any Grade 3 or 4 toxicity (except nausea):** decrease dose of both drugs by 20% or as clinically indicated.

3. **Renal Dysfunction:**

Creatinine Clearance (mL/min)	Topotecan Dose
greater than or equal to 40	100%
less than 40	not recommended

$$\text{CrCl (mL/min)} = \frac{N \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/L)}}$$

where N=1.04 for females and 1.23 for males

PRECAUTIONS:

1. **Myelosuppression** is a significant risk. Saylor’s Phase II clinical trial used topotecan 0.75 mg/m²/d x 5 days, with filgrastim support starting Day 6 until adequate neutrophil recovery. There was Grade 3/4 neutropenia in 53% of courses, and 44% of courses were complicated by Grade 3/4 thrombocytopenia.¹ This current protocol uses topotecan 0.5 mg/m²/d x 5 days without filgrastim support. However, if felt appropriate (i.e., dependent on review of prior therapy, renal status, performance status, etc) **AND** if filgrastim support is available, the oncologist may use the Saylor regimen. Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. Advise patients of importance of **adequate oral hydration** prior to and following chemotherapy.
3. Topotecan is a **radiation sensitizing agent**.⁴

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

REFERENCES:

1. Saylor III RL, Kimo C, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumours: a Pediatric Oncology Group Phase II Study. *J Clin Oncol* 2001;19(15):3463-9.
2. Humold A, Weddeling, N, Paulussen, M, et al. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. *Pediatr Blood Cancer* 2006;47:795-800.
3. Walterhouse, DO, Lyden, ER, Breitfeld PB, et al. Efficacy of topotecan and cyclophosphamide given in a phase II window trial in children with newly diagnosed metastatic rhabdomyosarcoma: a Children’s Oncology Group Study. *J Clin Oncol* 2004;22(8):1398-403.
4. Grabenbauer GG, Buchfelder M, Schrell U, et al. Topotecan as a 21 day continuous infusion with accelerated 3D-conformal radiation therapy for patients with glioblastoma. *Front Radiat Ther Onc* 1999;33:364-8.