BCCA Protocol Summary for Etoposide, Ifosfamide-Mesna (SAIME) Alternating with vinCRIStine, DOXOrubicin and Cyclophosphamide (with or without Mesna)(SAVAC or SAVACM) with Filgrastim Support at a TWO Weekly Intervals for Newly Diagnosed Ewing's Sarcoma/ Ewing's Family of Tumours, Desmoplastic Intra-abdominal Small Round Blue Cell tumour or Rhabdomyosarcoma

Protocol Code	*SAALT2W*
Tumour Group	*Sarcoma*
Contact Physician	*Dr. Meg Knowling*

ELIGIBILITY:

- Newly diagnosed Ewing's sarcoma/Ewing's family of tumours, intra-abdominal small round blue cell tumour or rhabdomyosarcoma or high grade small round blue cell tumours in the adolescent/young adult age group (less than 30)
- SAVACM to be used rather than SAVAC if pelvic radiation planned
- Normal kidney, cardiac and hepatic function

TESTS:

Before SAIME usually given Cycle day 1:

- Baseline and before each treatment: CBC & diff, platelets, lytes, phosphate, albumin, bilirubin, creatinine
- If Day 1 CBC and diff or creatinine levels are ABNORMAL, recheck CBC and diff or creatinine on Day 4. Notify MD of Day 4 results prior to administering chemotherapy on Day 5
- Urine dipstick for blood before each treatment and every 8 hours during treatment – if positive at any time, notify doctor and send urine sample for urinalysis for verification and accurate determination of hematuria - refer to supportive care protocol SCMESNA (follow SCMESNA (SAIME/SAAVIME3) pre-printed order)
- Imaging of primary site and any metastatic disease is done after three full alternations – approximately week 11 of protocol.

Before SAVAC/SAVACM usually Cycle Day 15:

- Baseline and before each treatment: CBC and diff, platelets, creatinine, bilirubin, AST, alk phos, GGT, LDH
- Urine dipstick for blood:
  SAVAC: before each treatment – if positive at any time, notify doctor and send urine sample for urinalysis for verification and accurate determination of hematuria – if hematuria verified, switch to SAVACM

SAVACM: before each treatment and every 8 hours during treatment – if positive at any time, notify doctor and send urine sample for urinalysis for verification and accurate determination of hematuria - refer to supportive care protocol SCMESNA (follow SCMESNA (SAVACM/SAVDCM) pre-printed order)

- If clinically indicated: ECG

PREMEDICATIONS:

SAIME

- Antiemetic protocol for high-moderate emetogenic chemotherapy protocols (see SCNAUSEA)

SAVAC/SAVAC+M

- Antiemetic protocol for high emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

7 full alternations of SAIME with SAVAC/SAVACM (14 chemotherapy administrations). SAVACM to be used rather than SAVAC if pelvic radiation planned

SAIME: Given daily for 5 consecutive days

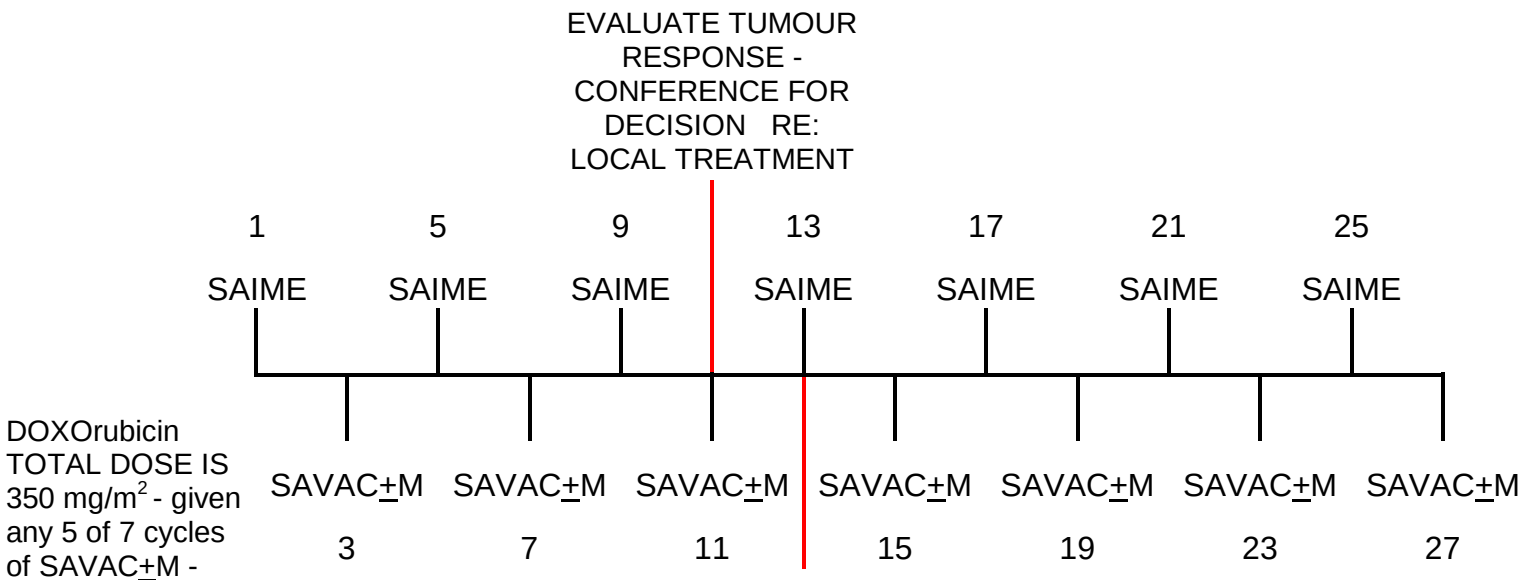
- Repeat **EVERY 4 WEEKS**, alternating with SAVAC or SAVACM every 2 weeks for total of 7 cycles (14 chemotherapy treatments). **Note** DOXOrubicin is generally given to a total dose of 375 mg/m² (5 cycles) – after that cumulative dose is reached then omit DOXOrubicin from SAVAC or SAVACM – giving only vinCRIStine and cyclophosphamide in the usual doses.
- **During radiation therapy (XRT)**. DOXOrubicin may be omitted from SAVAC or SAVACM depending on the location of the radiation. Sometimes SAIME may be repeated depending on clinical situation. DOXOrubicin is not reintroduced until at least three weeks after XRT has been completed.
- Filgrastim (G-CSF) to start Day 8 – Filgrastim may not be used to escalate doses beyond those specified in the protocol. The patient should be treated with filgrastim (G-CSF) in doses sufficient to allow full dose treatment on schedule using the dose modifications below. Note: this guideline applies only if the treatment is potentially curative and after experience with one or more cycles of treatment indicate filgrastim (G-CSF) is required. (See Pharmacare guidelines). Therefore alternate funding for first cycle is required.

SAIME

Hour	Drug	Dose	BCCA Administration Guide
0	etoposide	100 mg/m²	IV in 500 mL NS over 1 h (use non-DEHP equipment with in-line filter)
1	mesna	360 mg/m²	IV in 100 mL D5W over 15 min
	followed by		
	ifosfamide*	1800 mg/m^2	IV in 500 mL D5 ½ NS over 1 h
2.25 –9	After completion of Ifosfamide infusion: • For patients receiving MESNA orally, no further hydration needed. • For patients receiving MESNA by IV, continue hydration with D5 ½ NS IV at 250 mL/h until after Hour 9 Mesna.		
5 and 9	Mesna**	360 mg/m^2	IV in 100 mL D5W over 15 min
		or	
		720 mg/m²	PO in carbonated beverage as outpatient
9	D5 ½ NS IV at 150 mL/h for 8 hours • For patients who are hydrating well and have not had hematuria, IV hydration may be discontinued daily after Hour 9 Mesna bolus. • ONLY patients with hematuria requiring Mesna dose adjustments are required to be treated on a 24 hour schedule.		

* Total cumulative dose of Ifosfamide generally should not exceed 72 g/m² as there is an increased risk of Renal Fanconi Syndrome in children.
** If tolerated, may use oral mesna for last day of inpatient SAIME to allow for more timely discharge

ALTERNATING SAIME WITH SAVAC±M – **TWO** WEEKLY



DOXOrubicin TOTAL DOSE IS 350 mg/m^2 - given any 5 of 7 cycles of SAVAC±M - NOT during radiation of vital organs.

SURGERY - CHEMO is DELAYED; RESUME ALTERNATIONS once healed.
RADIATION - ALTERNATING CHEMO is CONCURRENT - but DO NOT GIVE DOXOrubicin in SAVAC±M if radiation will hit VITAL ORGANS. Restart DOXOrubicin 3 weeks AFTER COMPLETION RADIATION

SAVAC/SAVAC+M

- SAVACM rather than SAVAC to be used if pelvic radiation planned
- Repeat every 4 weeks, alternating with SAIME every 2 weeks.
- SAVAC/SAVACM is not usually given during radiotherapy unless the tumour is extremity primary. Protocol suggests dropping DOXOrubicin from SAVAC or SAVACM. SAIME may be repeated depending on clinical situation. DOXOrubicin is not reintroduced until at least three weeks after XRT has been completed.
- Admit for cycle one of SAVAC If well tolerated, subsequent cycles may be given as an outpatient in ACU providing patients on SAVACM can tolerate oral MESNA

SAVAC:

Drug	Dose	BCCA Administration Guideline
vinCRIStine	1.5 mg/m²	IV in 50 mL NS over 15 min (maximum dose = 2 mg)
DOXOrubicin*	75 mg/m^2	IV push
cyclophosphamide	1200 mg/m^2	IV in 500 mL D5W-1/2 NS over 1 hour

*Total cumulative dose should not exceed 375 mg/m².

SAVACM:

Drug	Dose	BCCA Administration Guideline
vinCRIStine	1.5 mg/m²	IV in 50 mL NS over 15 min (maximum dose = 2 mg)
DOXOrubicin*	75 mg/m^2	IV push
mesna	240 mg/m^2	Hour 0:30: IV in 100 mL D5W over 15 min
cyclophosphamide	1200 mg/m^2	IV in 500 mL D5W-1/2 NS over 1 hour
mesna	240 mg/m^2	Hours 5 and 8: IV in 100 mL D5W over 15 min *OR* 480 mg/m^2 PO in carbonated beverage

*Total cumulative dose should not exceed 375 mg/m².

HYDRATION for SAVACM:

Hours 1:45 to 11	IV D5W-1/2 NS at 250 mL/h
Hours 11 to 24	IV D5W-1/2 NS at 125 mL/h If no hematuria and patient is drinking well, IV hydration may be discontinued at Hour 15.

DOSE MODIFICATIONS for BOTH SAIME AND SAVAC/SAVACM:
If dose reduced, stay at reduced dose level for the rest of program.

1. **Hematological**: for treatment day counts reduce **ALL drugs**

ANC ($x10^9$/L)		**Platelets ($x10^9$/L)**	**Dose (ifosfamide, etoposide, DOXOrubicin, cyclophosphamide and mesna)**
greater than or equal to 0.75	and	greater than or equal to 100	Give 100%
less than 0.75	or	less than 100	Delay for 1 week* if counts recover then give 100% If counts do NOT recover by Day 22 - then reduce dose by 20% and continue with Q 2 weekly dosing if possible

*If unable to give full dose after 1 week delay – use dose reduction as indicated or consult Dr. Knowling

2. **Nausea and vomiting:** more than 10 episodes despite antiemetics and/or requiring parenteral fluid support, reduce dose of ALL DRUGS to 80%
3. **Hematuria:** If on SAVAC use SAVACM for subsequent cycles. If on SAIME or SAVACM, refer to SCMESNA
4. **Hepatic dysfunction:** Dose modifications may be required for DOXOrubicin and vinCRIStine (see BCCA Cancer Drug Manual)

5. **Renal Toxicity**: **SAIME:** If serum creatinine increases greater than 100% or greater than twice institutional normal at any time during treatment (measured Days 1 and 4), estimate creatinine clearance using formula:

$$\text{Creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine}}$$

* For males N= 1.23; For females N=1.04

   - If CrCl greater than 50mL/min, continue with ifosfamide. If CrCl less than 50mL/min, discontinue course. If ifosfamide is discontinued midcycle, continue with MESNA for 48 hours.
   - If renal function does not return to normal by next cycle, GIVE ETOPOSIDE AS A SINGLE AGENT.
   - **SAVAC/SAVACM:** Dose modification may be required for cyclophosphamide (see BCCA Cancer Drug Manual)

6. **CNS toxicity**: If drowsiness develops discontinue all sedating medications and continue ifosfamide. If patient is confused, unrousable or comatose, ifosfamide should be discontinued. If ifosfamide is the cause of CNS depression, then it should not be given again. If the CNS changes are not due to ifosfamide, then ifosfamide can be reinstituted providing the previous medications contributing to CNS changes are not given with it. If a seizure occurs while on ifosfamide, then that cycle is to be discontinued. Further cycles may be given if the patient is on anticonvulsants.
7. **Etoposide hypotensive reaction:** Stop etoposide infusion. Lie patient flat and run NS IV. Give diphenhydrAMINE 25 to 50 mg IV and hydrocortisone 100 mg IV. Resume etoposide infusion in 20 to 30 minutes, once patient is stable. For subsequent doses of etoposide, pre-medicate with diphenhydrAMINE 25 to 50 mg IV and hydrocortisone 100 mg IV.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Hypersensitivity**: Monitor infusion of etoposide for the first 15 minutes for signs of hypotension. Refer to BCCA Hypersensitivity Guidelines.
3. **Venous access**: ensure good venous access prior to starting ifosfamide so that MESNA can be given at completion of ifosfamide.
4. **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if lifelong dose of 375 mg/m^2 is exceeded (see BCCA Cancer Drug Manual).
5. **Extravasation:** DOXOrubicin and vinCRIStine cause pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.

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

Date activated: 1 Jun 2016

Date revised:

References:

1. Schuchter LM, Hensley ML, Meropol NJ, et al. 2002 Update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2002;20(12):2895-903.
2. Reaman G, Womer R, Krailo MD, Marina N. Memo: Chemotherapy for localized Ewing sarcoma: AEWS0031 results. In: Members C, editor. Arcadia, CA: COG; 2007. p. 1.
3. Womer RB, West DC, Krailo, MD et al. Randomized Controlled Trial of Interval-Compressed Chemotherapy for the Treatment of Localized Ewing Sarcoma: A Report From the Children's Oncology Group. J Clin Oncol 2012; 30:4148-4154.