

BCCA Protocol Summary for Etoposide, Ifosfamide-Mesna for Patients with Newly Diagnosed Ewing's Sarcoma/Peripheral Neuroectodermal Tumor (PNET) or Rhabdomyosarcoma or Advanced Soft Tissue or Bony Sarcomas (This may be alternated with SAVAC or SAVAC+M)

Protocol Code SAIME

Tumour Group Sarcoma

Contact Physician Dr. Meg Knowing

ELIGIBILITY:

- **For alternating program:** Newly diagnosed Ewing's sarcoma/PNET, intra-abdominal small round blue cell tumour or Rhabdomyosarcoma
- **For non-alternating program:** Advanced osteosarcoma after resection of metastases or in palliative situation or advanced soft tissue sarcomas
- **All patients:** Good performance status & normal bone marrow, liver and kidney function.

TESTS:

For both alternating and non-alternating groups:

- 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
- For patients with measurable disease, tumour response should be assessed prior to each treatment.
- Imaging to be done every SECOND treatment to monitor response in advanced disease setting.

PREMEDICATIONS:

- Ondansetron 8 mg PO/IV prechemo on Day 1, then 8 mg PO/IV q12h with Dexamethasone
- Dexamethasone 12 mg PO/IV prechemo on Day 1, then 4 mg PO/IV q12h with Ondansetron
- **Optional Ranitidine 150 mg PO bid**
- **Lorazepam 1mg SL every 4 to 6 hours as needed**
- **Prochlorperazine 10 mg PO/IV every 4 to 6 hours as needed**
- **Nabilone 1 mg PO every 6 to 8 hours as needed**
- **For Etoposide reaction: Hydrocortisone 100 mg IV and Diphenhydramine 50 mg IV as needed**

TREATMENT: Given daily for 5 consecutive days

- **For alternating program:** Repeat EVERY 6 WEEKS, alternating with SAVAC or SAVAC+M every 3 weeks. For young otherwise healthy patients, may repeat EVERY 4 WEEKS, alternating with SAVAC or SAVAC+M every 2 weeks. **During radiation therapy (XRT)** SAIME may be repeated until at least three weeks after XRT is completed.
- **For non-alternating program:** Repeat EVERY 3 WEEKS.

Hour	Drug	Dose	BCCA Administration Guide
0	Etoposide	100 mg/m ²	IV in 500 mL NS over 1 h (use non-PVC equipment)
1	Mesna	360 mg/m ²	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: <ul style="list-style-type: none"> • 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/m ²	PO in carbonated beverage as outpatient
9	D5 ½ NS IV at 150 mL/h for 8 hours <ul style="list-style-type: none"> • 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

DOSE MODIFICATIONS:

If dose reduced, stay at reduced dose level for the rest of program.

- Hematological:** for treatment day counts reduce **ALL drugs**

For alternating program: NOTE different phase reductions

A. During pre-XRT/pre-operative phase:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (ifosfamide and etoposide)
greater than or equal to 0.5	and	greater than or equal to 100	Give 100%
less than 0.5	or	less than 70	Delay for 1 week* (filgrastim should be considered if dose delay is required because of neutropenia)**

B. During XRT:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (ifosfamide and etoposide)
greater than or equal to 1.0	and	greater than or equal to 100	Give 100%
less than 1.0	or	less than 100	Delay for 1 week* (filgrastim should be considered if dose delay is required because of neutropenia)**

C. After XRT &/or operation:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (ifosfamide and etoposide)
greater than or equal to 0.75	and	greater than or equal to 100	Give 100%
less than 0.75	or	less than 70	Delay for 1 week* (filgrastim should be considered if dose delay is required because of neutropenia)**

*If unable to give after 1 week delay, consult Dr. Knowing for further dose modifications.

**Use of filgrastim (G-CSF) must be documented on the treatment form. 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 above dose modifications. 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)*

For non-alternating program:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (ifosfamide and etoposide)
greater than or equal to 1.5	and	greater than or equal to 100	Give 100%
1.0 – 1.5	or	70 – 100	In adjuvant setting, use filgrastim** otherwise give 80% (4 days)
less than 1.0	or	less than 100	Delay for 1 week*

*If unable to give after 1 week delay, consult Dr. Knowing for further dose modifications.

**Use of filgrastim (G-CSF) must be documented on the treatment form. 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 above dose modifications. 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)*

2. **Nausea & Vomiting:** more than 10 episodes despite antiemetics and/or requiring parenteral fluid support, reduce dose of ALL DRUGS to 80%
3. **Neutropenic Fever:** with ANC less than 0.5 x 10⁹/L, reduce dose of ALL DRUGS to 80%
4. **Hematuria:** See SCMESNA
5. **Renal Toxicity:** 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.
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 reinstated 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 25-50 mg IV and hydrocortisone 100 mg IV. Resume etoposide infusion in 20-30 minutes, once patient is stable. For subsequent doses of etoposide, pre-medicate with diphenhydramine 25-50 mg IV and hydrocortisone 100 mg IV.

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Extravasation:** Etoposide causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
3. **Hypersensitivity:** Monitor infusion of etoposide for the first 15 minutes for signs of hypotension. Refer to BCCA Hypersensitivity Guidelines.
4. **Venous access:** ensure good venous access prior to starting ifosfamide so that MESNA can be given at completion of ifosfamide.

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: 01 Apr 2003

Date revised: 1 Feb 2010 (premedications clarified)

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. Grier HE., Krailo MD, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone. *N Engl J Med* 2003;348(8): 694-701.
3. 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.