ELIGIBILITY:
- Advanced bone and adult or pediatric malignant connective tissue tumors
- All patients: Good performance status & normal bone marrow, liver and kidney function.

TESTS:
- Baseline and before each treatment: CBC & diff, platelets, creatinine, sodium, potassium, phosphate, bilirubin, alkaline phosphatase, LDH, albumin
- If Day 1 CBC and diff or creatinine levels are ABNORMAL, recheck CBC and diff or creatinine on Day 3. Notify MD of Day 3 results prior to administering chemotherapy on Day 3
- Urine dipstick for blood before each treatment as well as q 8 hours – if positive at any time, notify doctor, send urine sample for urinalysis for verification and accurate determination of hematuria and refer to supportive care protocol SCMESNA (switch to SAIME and follow SCMESNA (SAIME) preprinted order)
- For patients with measurable disease, tumour response should be assessed CLINICALLY prior to every cycle and by IMAGING every 2 or 3 cycles

PREMEDICATIONS:
- ondansetron 8 mg PO/IV 30 to 60 minutes pre-chemotherapy on Day 1, then 8 mg PO/IV every 12 hours for 5 doses
- dexamethasone 8 mg PO/IV 30 to 60 minutes pre-chemotherapy on Day 1, then 4 mg PO/IV every 12 hours for 5 doses
- Optional: netupitant-palonosetron 300 mg-0.5 mg PO 30 to 60 minutes pre-chemotherapy on Day 1. Ondansetron is not given pre- or post- chemotherapy if this option is chosen.
- ranitidine 150 mg PO bid (optional)
- 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: Days 1, 2 & 3 of a 21-day cycle

<table>
<thead>
<tr>
<th>Hour</th>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 1</td>
<td>etoposide</td>
<td>150 mg/m²</td>
<td>IV in 500 mL NS over 1 h (use non-DEHP equipment with in-line filter)</td>
</tr>
<tr>
<td>1 to 1.25</td>
<td>mesna</td>
<td>600 mg/m²</td>
<td>IV in 100 mL NS over 15 min</td>
</tr>
<tr>
<td>1.25 to 5.25</td>
<td>ifosfamide*†</td>
<td>3000 mg/m²</td>
<td>IV in 500 mL NS over 4 h To be y-sited</td>
</tr>
<tr>
<td></td>
<td>mesna†</td>
<td>1500 mg/m²</td>
<td>IV in 500 mL NS over 4 h</td>
</tr>
<tr>
<td>5.25 to 9.25</td>
<td></td>
<td></td>
<td>After completion of ifosfamide infusion:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- For patients receiving MESNA orally, no further hydration needed.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- For patients receiving MESNA by IV, continue hydration with NS IV at 250 mL/h until after Hour 9.25 mesna.</td>
</tr>
<tr>
<td>9.25 and 13.25</td>
<td>mesna**</td>
<td>600 mg/m²</td>
<td>IV in 100 mL NS over 15 min or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1200 mg/m² PO in carbonated beverage as outpatient</td>
</tr>
<tr>
<td>9.25</td>
<td>NS IV at 150 mL/h for 8 hours</td>
<td></td>
<td>For patients who are hydrating well and have not had hematuria, IV hydration may be discontinued daily after Hour 9.25 mesna bolus. ONLY patients with hematuria requiring mesna dose adjustments are required to be treated on a 24 hour schedule.</td>
</tr>
</tbody>
</table>

* Total cumulative dose of ifosfamide generally should not exceed 72000 mg/m² as there is an increased risk of Renal Fanconi Syndrome in children.
** If tolerated, may use oral mesna for last day of inpatient SAAVIME3 to allow for more timely discharge
† Ifosfamide and Mesna infused concurrently via Y-site connector placed immediately before injection site
DOSE MODIFICATIONS:
If dose reduced, stay at reduced dose level for the rest of program.

1. Hematological: for treatment day counts reduce ALL drugs

<table>
<thead>
<tr>
<th>ANC (x10^9 /L)</th>
<th>Platelets (x10^9 /L)</th>
<th>Dose (ifosfamide and etoposide)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.5 and greater than or equal to 100</td>
<td>Give 100%</td>
<td></td>
</tr>
<tr>
<td>1.0 to less than 1.5 or 70 to less than 100</td>
<td>In curative intent, use filgrastim** otherwise give 80%</td>
<td></td>
</tr>
<tr>
<td>less than 1.0 or less than 100</td>
<td>Delay for 1 week*</td>
<td></td>
</tr>
</tbody>
</table>

*If unable to give after 1 week delay, consult Dr. Simmons 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 10^9 /L, reduce dose of ALL DRUGS to 80%

4. Hematuria: See SCMESNA (switch to SAIME and follow SCMESNA(SAIME) preprinted order)

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 3), 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 is greater than 50mL/min, continue with ifosfamide. If CrCl is 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 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 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 BC Cancer Hypersensitivity Guidelines.

3. **Venous access:** ensure good venous access prior to starting ifosfamide so that MESNA can be given at completion of ifosfamide.

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**


