Ifosfamide for Ovarian Carcinosarcoma

Indication: Alternative Palliative chemotherapy to Carboplatin / Paclitaxel in Ovarian Carcinosarcoma when sarcoma elements predominate

Regimen details: Ifosfamide 2000mg/m² IV D1 – D3

Administration: Repeated daily for 3 days and starting at the same time each day

The scheduling is designed to ensure that there is adequate Mesna (uroprotective agent) in the bladder throughout the period when Ifosfamide metabolites are appearing in the urine

1 litre Sodium Chloride 0.9% IV over 2 hours, **on Day 1 ONLY**
Furosemide 40 mg orally

At hour 0

**Mesna** 400mg IV Bolus is given prior to each day Ifosfamide infusion (20% of total Ifosfamide dose)

Ifosfamide IV 2000mg/m² together with
Mesna IV 2000mg/m² in 1 litre Sodium Chloride 0.18% + Glucose 4% over 4 hours

Followed by either:

At hour 4

**Mesna** IV 1200mg/m² in 1 litre Sodium Chloride 0.9% over 12 hours

OR

At hour 2  **Mesna** 800mg/m² orally

At hour 6  **Mesna** 800mg/m² orally

Frequency: Every 21 days, for 6 cycles

Extravasation: Ifosfamide: Non- vesicant

Anti- emetics: Moderate emetogenic. Follow Local Anti-emetic Policy

Regular investigation:
- FBC D1
- U&Es D1
- LFTs D1
- Ca125 (if previously elevated) Every cycle
- EDTA Prior to 1st cycle

Comments: Hydration / Fluid balance – Ifosfamide

Weight should be recorded prior to and at the end of Ifosfamide treatment, and a strict fluid balance chart should be maintained. For low urine output, consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 - 2 kg, or symptoms of fluid overload or if there is an excessive positive fluid balance (> 1.5 L/Kg from the start of treatment)
Encephalopathy – Ifosfamide
Ifosfamide encephalopathy is a serious neurotoxic condition that can develop on any treatment cycle. In the early stages, it can present with a variety of symptoms such as somnolence, confusion and hallucinations. Any reports of patients being excessively drowsy or confused should be regarded as indicators of Ifosfamide encephalopathy. As this is a progressive condition, discuss with Consultant, discontinue Ifosfamide and institute treatment with Methylene blue (50mg IV four hourly) immediately. Seek Consultant advise

Three factors that have also been demonstrated to predispose individuals to this problem are renal impairment, low albumin and large pelvic tumour mass. If a patient has two of the three risk factors, consider discontinue Ifosfamide and institute appropriate supportive therapy. Future treatment needs to be reviewed by the Consultant

Nephrotoxicity – Ifosfamide
Renal function should be assessed by EDTA clearance, at the start of the treatment, but estimation from serum creatinine levels using the Cockcroft & Gault equation is acceptable if the patient has a stable creatinine concentration and no confounding factors (e.g. catabolic states). On subsequent cycles, EDTA needs to be re-assessed if there is a 30% change in serum creatinine

Haemorrhagic cystitis – Ifosfamide
A morning urine specimen should be examined before each scheduled dose of Ifosfamide because of the possibility of Ifosfamide – induced haemorrhagic cystitis. To decrease the incidence and severity of bladder toxicity, adequate hydration, maintenance of fluid balance and a uroprotective agent, Mesna, should be used. In patients who develop microscopic haematuria, despite concurrent use of Mesna, Ifosfamide therapy should be discontinued until the haematuria resolves

DOSE MODIFICATIONS
Haematological toxicity
Day1

WBC < 3.0 x 10^9/L or Neutrophils < 1.5 x 10^9/L or Platelets < 100 x 10^9/L
Delay for 1 week. Repeat FBC - If within normal parameters, resume all drugs with 100% doses

Subsequent cycles
Ifosfamide dose should be reduced to 1600mg/m2 if:

Neutrophils < 0.5 x 10^9/L for more than 1 week, OR
Febrile neutropenia is diagnosed, OR
Platelets < 50 x 10^9/L

Do not escalate for subsequent cycles. If the patient continues to experience these side effects at the lower dose, treatment should be discontinued
<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>GFR (ml/min)</th>
<th>Ifosfamide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>40 – 59</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Clinical decision</td>
<td></td>
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</tbody>
</table>

**Hepatic Impairment**

Ifosfamide is not recommended in patients with a bilirubin > 17µmol/L or serum transaminases or ALP > 2.5 x ULN. Discuss with Consultant

**Toxicities:**
- Myelosuppression
- Nausea
- Vomiting
- Mucositis
- Nephrotoxicity
- Neurotoxicity
- Encephalopathy
- Urotoxicity
- Haematuria
- Haemorrhagic cystitis
- Alopecia

**Drug interactions:**
- Ifosfamide
  - Phenobarbital: may enhance the risk of encephalopathy
  - Warfarin: anticoagulant effect of warfarin may be enhanced

**References:**

- [www.medicines.org.uk](http://www.medicines.org.uk)
- GSTT guidelines for treating nausea and vomiting in adult patients. September 2007
- UCLH- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009
- Stockley’s Drug Interactions. Interactions search: Ifosfamide. May’09
- CTCAE v3.0. August 2006