Regimen: Topotecan IV Classic 5 day schedule

Indications

1. Recommended as an option for second-line (or subsequent) treatment only for those women with platinum-refractory or platinum-resistant advanced ovarian cancer, or those who are allergic to platinum-based compounds, for whom pegylated liposomal doxorubicin hydrochloride and single-agent paclitaxel are considered inappropriate (NICE TA91).

2. Palliative therapy for relapsed ovarian, fallopian tube or primary peritoneal cancer

Regimen details

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 5</td>
<td>Topotecan</td>
<td>1.5mg/m² *</td>
<td>IV</td>
</tr>
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</table>

* This dose and schedule may be too toxic for some patients, especially those heavily pretreated with platinum-based therapy. In such patients, consider commencing topotecan at doses of 1.0-1.25mg/m²/day.

Two differing schedules exist. The modified weekly regimen (ASWCS09 GYN013) has been shown to be equivalent, less toxic and generally more convenient for patients than the licensed Classic 5-day schedule

Treatment options should be discussed with the patient although either regimen can be used.

Administration

Topotecan is administered as an intravenous infusion in 50-100mL sodium chloride 0.9% or glucose 5%. The final concentration of topotecan must be between 25 and 50 microgram/mL.

Topotecan is administered over 30 minutes.

Frequency

Every 21 days for a maximum of 6 cycles

Extravasation

Topotecan is an exfoliant (Group 4)

Premedication

None usually required

Emetogenicity

This protocol has moderate-low emetogenic potential – refer to local protocol.

Additional recommended supportive medication

Give written information sheet concerning diarrhoea. Take loperamide 4mg at the first loose stool and then 2mg every 2 hours until diarrhoea-free (for up to 48 hours). If it persists >24 hours, start Ciprofloxacin 500 mg bd.

Pre-treatment evaluation

- FBC: Baseline - results valid for 14 days
- LFT: Baseline - results valid for 14 days
- U&E (inc. SrCr): Baseline - results valid for 14 days
- Ca125: Pre D1 – results valid for 28 days
**Regular investigations**

- **FBC** Pre D1 – results valid for 72 hours
- **LFT** Pre D1 – results valid for 7 days
- **U&E (inc. SrCr)** Pre D1 – results valid for 7 days
- **Ca125** Pre D1 – results valid for 7 days
- **Clinical Assessment** Clinically assess patient prior to each cycle.

**Standard limits for administration to go ahead** – if blood results not within range, authorisation to administer must be given by prescriber/consultant

<table>
<thead>
<tr>
<th>Investigate</th>
<th>Limit</th>
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<tbody>
<tr>
<td>Neutrophil count</td>
<td>≥ 1.5 x 10^9/L</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>≥ 9 g/dL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>≥ 100 x 10^9/L</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>&gt; 40 ml/min</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt; 1.5 x ULN</td>
</tr>
<tr>
<td>ALT/AST</td>
<td>&lt; 1.5 x ULN</td>
</tr>
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</table>

**Dose modifications**

**Haematological toxicity**

Defer therapy for 1 week if neutrophils < 1.5 x 10^9/L OR platelets < 100 x 10^9/L.

Doses should be reduced in patients who experience any of the following:

- Neutrophils < 0.5 x 10^9/L for 7 days or more or severe neutropenia with fever or infection
- Treatment delay due to neutropenia
- Platelets < 25 x 10^9/L at any point after treatment

Any grade 4 neutropenia with a single oral temp > 38.5°C should result in administration of prophylactic antibiotics in all subsequent courses (e.g. ciprofloxacin 250-500 mg bd)

**Renal impairment**

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Topotecan Dose</th>
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<tbody>
<tr>
<td>≥ 40</td>
<td>100%</td>
</tr>
<tr>
<td>20-39</td>
<td>50%</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Contraindicated</td>
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</table>

**Hepatic impairment**

There is a lack of information available to guide dosing in patients with severely impaired hepatic function. The summary of product characteristics advises that topotecan is not recommended in patients with severely impaired hepatic function (bilirubin > 10 x ULN).

**NCI Common Toxicity Criteria**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Definition</th>
<th>Dose adjustment</th>
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<tbody>
<tr>
<td>Febrile neutropenia</td>
<td>ANC &lt; 0.5 x 10^9/L plus fever requiring IV antibiotics +/- hospitalisation</td>
<td>Reduce dose by 0.25 mg/m^2/day for all future doses.</td>
</tr>
<tr>
<td>Other toxicities</td>
<td>Grade 3 toxicity (except alopecia, nausea &amp; vomiting)</td>
<td>Reduce dose by 0.25 mg/m^2/day provided toxicity has resolved to Grade 1 or less. If further toxicity occurs, an additional reduction may be made after discussion with consultant</td>
</tr>
<tr>
<td></td>
<td>Grade 4 toxicity (except alopecia, nausea &amp; vomiting)</td>
<td>Withhold treatment and discuss with consultant</td>
</tr>
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</table>

If a delay of more than 3 weeks is required for recovery, or more than 2 dose reductions are necessary, the patient should discontinue treatment.
### Adverse effects

- **Rare or Serious Side Effects**
  - Interstitial lung disease (rare)
  - Paresthesia
  - Myelosuppression
  - Fatigue / asthenia
  - Abdominal pain
  - Anorexia

- **Frequently occurring Side Effects**
  - Nausea and vomiting
  - Constipation
  - Diarrhoea

- **Other**
  - Alopecia; headache; stomatitis; pruritis and rash

- *Treatment-emergent diarrhoea should be managed aggressively. Patients should be advised how to manage chemotherapy-induced diarrhoea, including, recognition of early warning signs, use of antidiarrheals and antibiotics, changes in fluid intake and diet, and the need for hospitalization.*

### Significant drug interactions

- **Warfarin/coumarin anticoagulants** Avoid if possible as use often causes an elevation or fluctuation in the INR – in the first instance consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

- **Clozpine** increases the risk of agranulocytosis; avoid concomitant use.

- **Digoxin tablets**: reduced absorption (resolved by giving the digoxin in liquid form).

- **P-glycoprotein inhibitors** (cyclosporin, ketoconazole, ritonavir, saquinavir): cause increased exposure of topotecan.

- **Phenytoin** may increase topotecan clearance.

### Comments

None

### Cumulative Doses

None

### References

- Summary of Product Characteristics Hycamtin 1mg and 4mg powder for concentrate for solution for infusion (GlaxoSmithKline UK) [internet] accessed 6/6/10 available from http://www.medicines.org.uk/EMC/medicine/15277/SPC

<table>
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<th>Document title</th>
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<tr>
<td>Document number</td>
<td>ASWCS09 GYN012</td>
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<tr>
<td>Approval date</td>
<td>22/01/2012</td>
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<tr>
<td>Written by</td>
<td>Paul Cornes, Consultant Clinical Oncologist, BHOC</td>
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<tr>
<td>Checked by</td>
<td>James Carr, Network Pharmacist, ASWCS</td>
</tr>
<tr>
<td>Authorised by</td>
<td>Jeremy Braybrooke, Chair, ASWCS Network Chemotherapy Group</td>
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<tr>
<td>Review date</td>
<td>January 2014</td>
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<tr>
<td>Version number</td>
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