Proposed medicines(s) for treatment of Ovarian Germ Cell Tumors (refer to application for specific protocols):

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Currently on EML</th>
<th>Addition</th>
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<tbody>
<tr>
<td>bleomycin</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>etoposide</td>
<td>✗</td>
<td></td>
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<tr>
<td>cisplatin</td>
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<td>✗</td>
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<tr>
<td>paclitaxel</td>
<td>✗</td>
<td></td>
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<tr>
<td>ifosfamide</td>
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<tr>
<td>mesna</td>
<td>✗</td>
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<tr>
<td>G-CSF</td>
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(1) Does the application adequately address the issue of the public health need for the treatment of the disease?

√ Yes ☐ No ☐

Comments: As ovarian germ cell tumours occur in young women between 15 and 30 year old and are lethal if left untreated, there is a public health need for access to chemotherapy drugs which enable cure of disease.

(2) Have all important studies that you are aware of been included in the application?

√ Yes ☐ No ☐

Comments:

1. It would be worthwhile adding the study of Segelov and colleagues in support for BEP efficacy. In the study by Segelov et al, the overall survival at 5 years for all patients was 87% (92% for those with dysgerminomas and 85% for non dysgerminomas). The study enrolled 58 patients.


2. It would be worthwhile adding the study of Mead and colleagues (2005) in support for efficacy of TIP as salvage chemotherapy.

3. It would be worthwhile adding the study of Aapro and colleagues (2006) in support for routine use of G-CSF with BEP.


(3) Does the application provide adequate evidence of efficacy/effectiveness of the proposed treatment regimen(s)?

√ Yes □ No □

Comments: In addition, in the study by Segelov et al, the overall survival at 5 years for all patients was 87% (92% for those with dysgerminomas and 85% for non-dysgerminomas).

(4) Does the application provide adequate evidence of safety for the proposed treatment regimen(s)? Are there any adverse effects of concern, or that may require special monitoring?

√ Yes □ No □

Comments:

Other potential side effects which may need monitoring:

1. Ototoxicity
   Cisplatin induced ototoxicity may occur; patients should be monitored for signs and symptoms.

2. Peripheral neuropathy
   Assess prior to each cycle. If a patient experiences > grade 2 a dose reduction or delay of treatment may be required; review by medical officer before commencing treatment.

3. Pulmonary function
   Baseline clinical assessment and pulmonary function tests (including DLCO), repeat with each cycle.

4. Chest x-rays may be considered where clinically indicated.
5. Blood tests
Blood tests: Baseline and repeat prior to each cycle FBC, EUC, LFTs, calcium and magnesium. For cycle 1, repeat EUC on day 8.

Note. In addition, cisplatin is a highly emetogenic agent. Correct anti-emetic regimen needs to be prescribed with the chemotherapy (Ondansetron, dexamethasone).

Additional monitoring for TIP chemotherapy
For paclitaxel, it is important to monitor for neurotoxicity and dose reduce or omit if significant neuropathy occurs.

For ifosfamide, it is important to monitor for bladder toxicity and neurotoxicity.

Ifosfamide infusion

Prior to administration
- assess neurological function at baseline and prior to each ifosfamide dose
  - Inpatients: 4 hourly assessments until 24 hours after ifosfamide infusion is completed
  - Outpatients: advise patient/carer of the potential for neurotoxicity
- perform baseline urinalysis and monitor for haematuria prior to each ifosfamide dose (note the administration of mesna will cause a false positive for ketonuria)

ADDITIONAL CONSIDERATIONS:

(5) Are there special requirements or training needed for the safe, effective and/or appropriate use of the proposed treatment(s)?

√ Yes  □  √ No  □

Comments:

Patients should be preferably treated in centers that are experienced in the management of germ cell tumours.
Medical Oncologists only can prescribe and supervise chemotherapy for ovarian germ cell tumours. Chemotherapy –trained nurses only can administer the drugs.

(6) Are there any issues regarding the registration of the proposed medicines by regulatory authorities? (e.g., recent registration, new indications, off-label use)

Yes  □  √ No  □

Comments: Not that we are aware.
(7) **Comment briefly on issues regarding cost and affordability of treatment.**

As drugs used in BEP regimen are off patent use and widely used in treatment of testicular cancer, which is ten times more common, the cost and affordability of treatment should not pose any additional significant burden on the health systems of different countries, especially as its aim is to treat a rare and potentially curable disease of the young women.

(8) **Any additional comments on the application?**

In view of equity, these life-saving treatments for germ cell tumours should be made equally accessible to young females as they are already available for young males.

(9) **Please summarise the action(s) you propose the Expert Committee take.**

Ensure that Cisplatin and G-CSF are added on the WHO of essential medicine for treatment of ovarian germ cell tumours in females.