OVARIAN GERM CELL TUMORS
Union for International Cancer Control
2014 Review of Cancer Medicines on the WHO List of Essential Medicines

OVARIAN GERM CELL TUMORS

Executive Summary

Ovarian germ cell tumors (OGCTs) are derived from primordial germ cells of the ovary. These tumors affect both adults and children and therefore the recommendations apply to the EML lists for both adults and children (regimen distinctions are included in the present briefing).

OGCTs include dysgerminomas and nondysgerminomas, which are subdivided to immature teratoma, embryonal cell carcinoma, yolk sac tumors, primary ovarian (nongestational) choriocarcinomas, polyembryoma, and mixed germ cell tumors. OGCTs comprise of 2-3% of all malignant ovarian tumors registered globally, with highest rates in young women of 15 to 30 years old [1]. Since 1990, the standard regimen for OGCT treatment has been a combination of bleomycin, etoposide and cisplatin, referred to as “BEP” regimen. The standard of care in the United States, Europe, and other high-income settings is a combination of the three chemotherapy agents plus surgery. This allows to achieve a survival rate of 95-100% at 5 years among patients receiving adjuvant BEP regimen after surgery for stage I disease, and 70-85% among patients with metastatic disease (II-IV stages) on BEP regimen [2,3]. The chance of survival without chemotherapy is 0%. Addition of filgrastim to chemotherapy when a patients’ absolute neutrophil count decreases to less than 500 prevents the occurrence of severe neutropenia and infection. Using filgrastim helps to maintain appropriate dose intensity, which is vital in the treatment of germ cell tumors, as well as other curable tumors.

Thus, with the addition of BEP regimen to surgery, a gain in survival from 0% to 85% is achieved. Drugs used in BEP regimen are off-patent drugs and also used in the treatment of testicular cancer which is up to ten times more common than OGCTs. We have four recommendations: (1) to add filgrastim to the Essential Medicines List for cytotoxics; (2) to list cisplatin separately from carboplatin in the cytotoxics section; (3) to add diphenhydramine to the list of adjuvant medicines for cancer; and (4) to add ranitidine to the cytotoxics section in addition to its current place on the antiulcer section of the List. All other drugs are already listed.

Public Health Relevance

OGCT is a rare disease in adult cancer overall, but is the one of the common solid malignancies among women between 15 and 30 years old. According to the United States National Cancer Institute’s SEER Database, the 30-year, age-adjusted incidence rate per 100,000 women-years was 0.338, decreasing by 29.4% for dysgerminomas and by 31.5% for mixed OGCTs [4]. The incidence rates were higher for Asian/Pacific Islanders and Hispanics. Although global epidemiological data on OGCT burden are limited, the combined knowledge generated from discrete studies warrants urgent action to expand access to chemotherapy drugs. International Agency for Research on Cancer in Globocan only reports incidence of cancer by site and not
histology, therefore one cannot differentiate rates of OGCTs from other malignant ovarian tumors. Epidemiological data from various national databases [4,5] support the conclusions that the burden of OGCTs is not confined to high-income settings. Therefore the treatment options must be made available internationally.

Requirements for diagnosis, treatment, and monitoring

**Diagnostics:** Pathomorphological analysis of surgically resected ovarian tumor is required. Elevated tumor serum markers (alpha-fetoprotein (AFP) and/or beta-human chorionic gonadotropin (b-hCG)) assist in making the correct diagnosis preoperatively.

**Testing:** The final stage is assigned after surgery, where the tumor burden in abdomen is assessed in accordance with FIGO (The International Federation of Gynecology and Obstetrics) classification. Pre-surgical tests include AFP, b-hCG and LDH (Lactate Dehydrogenase), chest X-Ray, abdomen and pelvic ultrasound (or contrast enhanced computed tomography scan), and blood counts and chemistries to assess critical organ function, including renal and hepatic function.

**Administration and Care of Patients:** Patients should be preferably treated in centers that are experienced in the management of germ cell tumors. Typically, cytoreductive fertility-sparing surgery, which includes unilateral salpingo-oophorectomy, is the first step of the treatment. It is critical to also examine the peritoneal fluid (either ascetic fluid or peritoneal washings) to ascertain whether there is evidence of spread outside the ovary. Twenty-five percent of patients who would otherwise be classified as stage I have positive peritoneal cytology. Treatment decisions are based on the pathological stage, residual tumor and tumor histology. Further treatment options include active observation for Stage I patients or three to four cycles of BEP regimen for stage II-IV patients. Cisplatin intravenous infusions require in-patient facilities, as it is accompanied with prolonged intravenous hydration, forced diuresis and anti-emetics. Filgrastim is administered subcutaneously between cycles of chemotherapy. Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, pulmonary toxicity, renal toxicity and gastrointestinal toxicity. Social and financial wellbeing can be impacted by treatment side effects and should be monitored and addressed as well. Patients who have residual tumor after treatment with chemotherapy ought to undergo secondary surgery so that all residual tumor lesions are excised. Notably, patients should not have second look surgery unless there is evidence of residual disease after chemotherapy. For low-resource settings, if a patient has had inadequate staging, it is not recommended that a second surgery be undertaken. Rather, the patient should be given chemotherapy and assessed after treatment to resect residual disease.
Overview of Regimens

The administration and dosing schedule for BEP and TIP are described below. The regimens are the same for both adult and pediatric patients. Three cycles of BEP regimen should be administered to patients with Stage II/III disease and four cycles to patients with stage IV disease. Cycles should be repeated every 3 weeks. Treatment compliance and maintenance of treatment intensity is vital. Filgrastim is used subcutaneously on outpatient basis for 5-7 days after completion of every cycle.

Essential Regimens

**BEP (ADULT)**: 2-4 cycles every 3 weeks (1st line treatment)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Intravenous bolus</td>
<td>30 mg on days 1, 8, 15</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Intravenous infusion</td>
<td>100 mg/m² on days 1,2,3,4,5</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Intravenous infusion</td>
<td>20 mg/m² on days 1,2,3,4,5</td>
</tr>
</tbody>
</table>

**BEP (PREPUBERTAL CHILDREN)**: 2-4 cycles every 3 weeks (1st line treatment)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Intravenous bolus</td>
<td>15 U/m² on day 1; max. dose 30U</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Intravenous infusion</td>
<td>100 mg/m² on days 1,2,3,4,5</td>
</tr>
<tr>
<td>Cisplatin*</td>
<td>Intravenous infusion</td>
<td>20 mg/m² on days 1,2,3,4,5</td>
</tr>
</tbody>
</table>

*For BEP, an accepted substitution for cisplatin among prepubertal children is carboplatin with a dose of AUC 7.9. This has less renal toxicity.

**TIP**: 4 cycles every 3 weeks in patients with recurrent disease (2nd line treatment)

**Premedication**

- **Dexamethasone**: 20mg orally approximately 14 (12-24) hours and 7 (6-9) hours before paclitaxel (taken by the patient at home the night before and morning of day 1) or 20 mg IV 30-60 minutes prior to initiation of the paclitaxel infusion.

- **Diphenhydramine**: 25mg IVPB 30-60 minutes prior to paclitaxel. Oral can be substituted but must be given 60 minutes prior to paclitaxel. An equivalent H1 blocker (e.g., hydroxyzine) can be substituted for diphenhydramine.

- **H2 blocker**: Ranitidine, Cimetidine, and Famotidine are acceptable, given oral 60 minutes prior or by IVPB 30-60 minutes prior to paclitaxel.

*These drugs have not been included as specific anti-cancer medicines as they are used for other disease categories in the EML and are supportive medicines.
TIP (cont’d)

**Paclitaxel**
24 hours intravenous infusion
250 mg/m² over 24 hours day 1

**Ifosfamide**
Intravenous infusion
1500 mg/m² days 2,3,4,5

**Mesna**
Bolus, given to match the ifosfamide dose, either mixed 1:1 with ifosfamide or pre- or post-ifosfamide and hydration.
1500 mg/m² days 2,3,4,5

**Cisplatin**
Intravenous infusion
25 mg/m² days 2,3,4,5

**Filgastrim (if pegylated GCSF unavailable)**
subcutaneously
5 mcg/kg (3-7 mcg/kg acceptable) subcutaneously daily from day 7 to day 18, or recovery of absolute neutrophil count to greater than 1000/mm³ (whichever occurs first)***

* G-CSF should be discontinued 24h prior to starting the next chemotherapy treatment.

**Review of Benefits and Harms**

**Benefits**
Given that patients diagnosed with stage II-III OGC who do not receive treatment cannot survive, the survival benefit obtained from the Essential Regimen BEP is of utmost importance.

Despite greater efficacy of BEP regimen, around 15% of patients relapse. Using TIP regimen as second line can cure up to 65% of these patients [10].

**Harms and Toxicity Considerations**

**Common**
Patients receiving BEP will suffer alopecia and myelosuppression, particularly neutropenia that increases the risk of infection. However, the incidence of serious infections in these patients is low.[8]

Renal toxicity with cisplatin is common, close monitoring of routine labs and aggressive IV hydration are necessary to avoid significant declines in renal function. With prophylactic hydration, reductions in GFR occurs in 20-30% of patients on cisplatin. [11]
The toxicities associated with this regimen can be significant, including risks for acute- and later-onset pulmonary toxicity associated with bleomycin and a minimal but increased risk of treatment-related myeloid neoplasms with etoposide.[12]

Bleomycin dosed in the regimens above is essentially devoid of any clinically significant pulmonary toxicity [8,13]. However, the risk of toxicity is dose-dependent (increasing with cumulative doses above 400 units) and patients should be closely monitored at each visit for respiratory lag or rales which can be a sign of early bleomycin-induced pulmonary disease. In the absence of pulmonary function tests, any rales (especially in lung bases) that do not clear with coughing are an indication to stop bleomycin therapy.

Systematic Reviews
The following systematic reviews and meta-analyses summarize the literature supporting the use of BEP and TIP for the treatment of metastatic OGCTs.


Abstract: Most women diagnosed with malignant ovarian germ cell tumors have curable disease and experience excellent survival with manageable treatment-associated morbidity, related both to tumor biology and improvements in treatment over the last 4 decades. Malignant ovarian germ cell tumors occur predominantly in girls, adolescents, and young women and are often unilateral tumors of early stage, although advanced-stage disease occurs in approximately 30% of patients. Tumors are usually chemosensitive, thereby allowing fertility-sparing surgery in most women with high chance of cure. Differences in practice do exist among providers in various subspecialties and geographic areas. In most settings, collaborative efforts among specialties allow the optimal treatment of women with these rare tumors, and implementation of standard guidelines at an international level should translate to effective clinical trial design, rapid accrual to clinical trials, and universally improved patient outcomes. This consensus guideline represents a summary of recommendations for diagnosis and management that has been agreed upon by cooperative groups worldwide. It builds upon individual publications including previously published summary documents and provides the most current practice standards validated worldwide.
Recommendations

The reviewers recommend the incorporation of ovarian germ cell tumor treatment options into the WHO Model List of Essential Medicines, and recommend specifically that cisplatin and G-CSF be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

Cisplatin*
G-CSF**

*Note: Carboplatin is currently on the EML but there are therapeutic differences between the platinum agents, cisplatin, carboplatin and oxaliplatin and they cannot be considered class agents but should be approved with specific indications.

** Please refer to the supplemental document on granulocyte colony-stimulating factors that is appended to the overall proposal for details on the use of G-CSF
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References