Ovarian germ cell tumours – EML and EMLc

The application sought endorsement of the following medicines, currently included on the complementary list of the Model List of Essential Medicines for the treatment of ovarian germ cell tumours: bleomycin, etoposide, paclitaxel, ifosfamide and mesna. The application also sought the addition of cisplatin and granulocyte colony-stimulating factor (G-CSF, filgrastim) to the core list for use in this indication. As ovarian germ cell tumours (OGCTs) affect both adults and children, the application proposed inclusion of these medicines in the both the EML and EMLc.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Ovarian germ cell tumours (OGCTs) are derived from primordial germ cells of the ovary. They are highly malignant and rapidly growing tumours that affect both adults and children, with peak incidence occurring in adolescent girls and young women *(1)*. Incidence varies geographically: OGCTs account for less than 5% of malignant ovarian tumours in developed countries, but up to 15% among Asian and black populations *(1)*.

OGCTs are broadly classified into two types – dysgerminomas and non-dysgerminomas. Non-dysgerminomas are further divided into a number of subtypes: immature teratoma, embryonal cell carcinoma, yolk sac tumours, primary ovarian (non-gestational) choriocarcinomas, polyembryoma, and mixed germ cell tumours *(2)*.

Surgery is the initial treatment, to establish the diagnosis and staging and to remove or optimally debulk the tumour. Fertility-sparing surgery is the standard procedure in young women wherever possible *(1)*. For patients with stage IA dysgerminoma or stage IA, grade 1 immature teratoma, treatment is with surgery alone: rates of recurrence are low. Postoperative chemotherapy is used in most other cases.

Before the introduction of combination chemotherapy, survival from OGCTs was negligible *(2)*. However, OGCTs have proved to be highly chemosensitive and, since 1990, the standard postoperative chemotherapy regimen has been bleomycin, etoposide and cisplatin (BEP) *(3)*. Surgery plus BEP has been associated with survival rates of 95–100% at 5 years among patients with early-stage disease and 75–80% among those with advanced disease *(1, 4, 5)*. A significant survival gain is thus achieved by adding the BEP regimen to surgery. Drugs used in the BEP regimen are off-patent and are also used in the treatment of testicular germ cell tumours, which are much common than OGCTs.

Public health relevance

OGCT is a rare disease in adult cancer overall but is the one of the common solid malignancies among women aged between 15 and 30 years. According to the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, the 30-year, age-adjusted incidence rate per 100 000 woman–years is 0.338, decreasing by 29.4% for dysgerminomas and by 31.5% for mixed OGCTs *(2)*. Incidence rates were higher for Asians, Pacific Islanders and Hispanics. Although global epidemiological data on OGCT burden are limited, the combined evidence from discrete studies warrants urgent action to expand access to chemotherapy drugs. In its GLOBOCAN analysis, the International Agency for Research on Cancer reports incidence of cancer only by site and not by histology, making it impossible to differentiate rates of OGCTs from those of other malignant ovarian tumours. Epidemiological data from various national databases support the conclusions that the burden of OGCTs is not confined to high-income settings.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Pathomorphological analysis of surgically resected ovarian tumour is required. Elevated tumour serum markers (alpha-fetoprotein, beta-human chorionic gonadotropin, lactate dehydrogenase) assist in making the correct diagnosis preoperatively.

Testing

The final stage is assigned after surgery, where the tumour burden in abdomen is assessed in accordance with FIGO (International Federation of Gynecology and Obstetrics) classification. Presurgical tests include tumour markers, chest X-ray, abdominal and pelvic ultrasound (or contrast-enhanced computerized tomography scan), and blood counts and chemistries to assess critical organ function, including renal and hepatic function.

Administration and care of patients

Patients should preferably be treated in centres that are experienced in the management of germ cell tumours. Typically, cytoreductive fertility-sparing surgery, which includes unilateral salpingo-oophorectomy, is the first step of the treatment. It is also critical to examine the peritoneal fluid (either ascitic 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 tumour and tumour histology. Further treatment options include active observation for patients with stage I disease or three to four cycles of BEP for those with stage II–IV.

Intravenous cisplatin infusions require inpatient facilities, since prolonged intravenous hydration, forced diuresis and antiemetics are also necessary. 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, and pulmonary, renal and gastrointestinal toxicity. Social and financial well-being can be impacted by the side-effects of treatment and should also be monitored and addressed.

Patients who have residual tumour after treatment with chemotherapy should undergo secondary surgery so that all residual tumour lesions are excised. Second-look surgery following complete response to primary surgery and chemotherapy is not routinely recommended *(6, 7)*. 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 is described below. Three cycles should be administered to patients with stage II–III disease and four cycles to patients with stage IV. Cycles should be repeated every 3 weeks. Treatment compliance and maintenance of treatment intensity is necessary.

Standard regimens – first line treatment

- **BEP – adult (21-day cycle; 3 or 4 cycles)**
  - bleomycin 30 U IV bolus on days 1, 8, 15
  - etoposide 100 mg/m^2 IV infusion on days 1–5
  - cisplatin 20 mg/m^2 IV infusion on days 1–5

- **BEP – prepubertal children (21-day cycle; 3 or 4 cycles)**
  - bleomycin 15 U/m^2 (max. 30 U) IV bolus on day 1
  - etoposide 100 mg/m^2 IV infusion on days 1–5
  - cisplatin[1] 20 mg/m^2 IV infusion on days 1–5

Standard regimens – salvage therapy (previously treated patients)

- **VeIP (21-day cycle; 4 cycles)**
  - vinblastine 0.11 mg/kg IV infusion on days 1 and 2
  - ifosfamide 1.2 g/m^2 IV infusion on days 1–5
  - cisplatin 20 mg/m^2 IV infusion on days 1–5

- **TIP (21-day cycle; 4 cycles)**
  (Premedications pertaining to the administration of paclitaxel are not shown.)
  - paclitaxel 250 mg/m^2 IV infusion over 24 hours on day 1
  - ifosfamide[2] 1.5 g/m^2 IV infusion on days 2–5

[1] An accepted substitution for cisplatin among prepubertal children is carboplatin at a dose of AUC 7.9, which has less renal toxicity.

[2] Administration of ifosfamide requires the accompanying drug, mesna.

– cisplatin25 mg/m^2 IV infusion on days 2–5

G-CSF (5 μg/kg) may be administered by subcutaneous injection daily from days 7 to 18, or until recovery of absolute neutrophil count to greater than 1000/mm^3 (whichever occurs first). It should be discontinued 24 hours before starting the next chemotherapy treatment.

Review of benefits and harms

Benefits

The rarity of ovarian germ cell tumours has meant there are no randomized controlled trials (RCTs) of treatments. Experience from RCTs for the more common testicular germ cell tumours has been extrapolated to the OGCT setting and has provided an evidence base for treatment decisions *(8)*.

Cisplatin-based chemotherapy for OGTC has been associated with survival rates ranging from 87% to 96%. A retrospective Australian study sought to evaluate cisplatin-based treatment of OGCT with regard to survival and toxicity *(9)*. The authors concluded that cisplatin-based chemotherapy for OGCT is highly effective, with 5-year overall survival of 87% based on data obtained from 58 patients. A prospective trial by the Gynecologic Oncology Group established postoperative chemotherapy with three cycles of BEP as the standard treatment for OGCTs *(10)*. This study reported 96% disease-free survival at a median follow-up of 38.6 months. In another prospective study of 48 patients with stage I–IV OGCTs, patients were administered a modified 3-day BEP regimen of either three or four cycles depending on disease staging. In this study, disease-free survival at five years was also 96% *(11)*.

Given that patients diagnosed with stage II–III OGCT who do not receive treatment cannot survive, the survival benefit obtained with BEP chemotherapy is highly relevant.

Despite the efficacy of BEP regimen, around 15% of patients relapse. Second-line salvage treatment with cisplatin, ifosfamide and either vinblastine (VeIP) or paclitaxel (TIP) has achieved cure in up to 65% of patients who relapse following first-line treatment *(12-14)*.

Harms and toxicity considerations

Common

Patients receiving BEP will suffer both alopecia and myelosuppression – particularly neutropenia, which increases the risk of infection. However, the incidence of serious infections in these patients is low *(11)*.

Renal toxicity with cisplatin is common. Close monitoring of routine laboratory tests and aggressive intravenous hydration are necessary to avoid significant decline in renal function. With prophylactic hydration, reductions in glomerular filtration rate occur in 20–30% of patients treated with cisplatin *(15)*.

Administration of paclitaxel is associated with hypersensitivity reactions, and prophylactic pretreatment with dexamethasone and H1- and H2-receptor antagonists is recommended *(16)*.

Serious

The toxicities associated with BEP 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 associated with etoposide *(17)*.

Bleomycin at the doses used in the regimens above is essentially devoid of any clinically significant pulmonary toxicity *(11, 18)*. However, the risk of toxicity is dose-dependent, increasing with cumulative doses above 400 units, and patients should be closely monitored 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.

Recommendations

The Expert Committee noted the available evidence for high cure rates associated with the proposed chemotherapy regimens for ovarian germ cell tumours and recommended the addition of cisplatin to the complementary list of the Model List of Essential Medicines and the Model List of Essential Medicines for Children and the endorsement of bleomycin, etoposide, ifosfamide, paclitaxel and vinblastine on both lists for treatment of OGCT. Additionally, given the requirement for treatment with ifosfamide to be accompanied by mesna, the Committee recommended inclusion of mesna on the complementary lists of the EML and EMLc for this indication.

The inclusion of G-CSF on the EML and EMLc was considered by the Expert Committee in a separate application.

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