Testicular 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 testicular germ cell tumours: bleomycin, etoposide, 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.

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

Introduction

Testicular germ cell tumours account for approximately 1% of all newly diagnosed male cancers worldwide, and in 2012 there were estimated to be more than 10 000 deaths from this disease (1). Testicular cancer is most commonly seen in young men but can also be seen in paediatric patients; the benefits of therapy are similar in the two age groups.

Testicular germ cell tumours are divided into two groups, seminomas and non-seminomas, with non-seminomas being further subdivided into four distinct histologies (yolk sac tumour, choriocarcinoma, embryonal cell carcinoma, and teratoma) (2). Approximately 95% of germ cell tumours arise in the testes, although extragonadal primary tumours of the retroperitoneum, mediastinum and pineal gland do occur (3). While most extragonadal tumours are more challenging to treat, germ cell tumours generally have an excellent overall prognosis, with 5-year survival rates in excess of 95% in developed countries. Cure rates for clinical stage I tumours approach 100%, and even patients who present with distant metastatic disease have impressive rates of long-term overall survival when treated with appropriate chemotherapy (4).

Management options for stage I patients include aggressive surveillance or radiation for seminoma, and surveillance, retroperitoneal lymph node dissection (RPLND) or short-course chemotherapy for non-seminoma. In addition to radical inguinal orchectomy, the backbone of standard therapy includes cisplatin-based combination chemotherapy, most often bleomycin, etoposide and cisplatin (BEP). The duration of treatment is based on stratification of advanced-disease patients into three risk groups – good risk, intermediate risk and poor risk – based on pathology, degree of tumour marker elevation (alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (β-hCG) and lactate dehydrogenase (LDH)) and imaging. In good-risk disease, either three cycles of BEP or four cycles of a combination of etoposide and cisplatin (EP) can be given with similar efficacy (5-11). In poor-risk disease, patients should receive four cycles of BEP or, for those with baseline lung disease, the alternative regimen of etoposide, ifosfamide and cisplatin (VIP) which has shown similar efficacy but with increased haematological toxicity (12, 13).

Salvage surgery also plays a major role in the treatment of these patients, and surgical resection should be considered in the setting of radiographically persistent disease with normal tumour markers as this may represent teratoma, which is not chemosensitive,
or residual viable cancer. This surgery is not recommended outside specialized centres of excellence, not typically seen in most low- and middle-income countries (LMICs). In patients with advanced disease, the combination of the above therapies gives approximate cure rates of over 90% for good risk, 75% for intermediate risk and 50% for poor risk status (14).

Public health relevance

Epidemiological information concerning germ cell tumours of the testes is limited. However, more than 90% of testicular cancers develop in germ cells, so epidemiological data for testicular cancer is a close approximation. For 2012, GLOBOCAN estimated the worldwide incidence of testicular cancer to be 55 266 (age-standardized rate (ASR) 1.5 per 100 000) (1); incidence in more developed regions was 32 740 (ASR 5.2 per 100 000) and in less developed regions 22 526 (ASR 0.7 per 100 000). In LMICs, the incidence of testicular cancer is far less, with a cumulative lifetime risk similar to that of Hodgkin lymphoma, melanoma and multiple myeloma (15).

GLOBOCAN estimated global mortality rate due to testicular cancer in 2012 to be 10 351 (ASR 0.3 per 100 000). Mortality rates in more developed regions (2209; ASR 0.4 per 100 000) and less developed regions (8142; ASR 0.3 per 100 000) were comparable. In developed countries testicular cancer is the most commonly diagnosed malignancy in men aged 15–40 years (16). Given that the disease is highly curable, improved outcomes are important both medically and economically because of the number of productive life-years gained with treatment.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

Initial evaluation of a suspicious testicular mass should include a complete history and physical examination, tumour markers including AFP, β-hCG and LDH, blood chemistries, a chest X-ray and testicular ultrasound. Trans-scrotal illumination may differentiate solid masses from hydroceles but cannot be used to rule out cancer because 20% of patients with testicular cancer have associated hydroceles. If a hypo-echoic testicular mass is found on ultrasound, radical inguinal orchiectomy is recommended since approximately 95% of these lesions are malignant. Scrotal biopsy is not advised – most masses are malignant and biopsy can result in seeding of the biopsy tract with malignant cells (14). Pathology will distinguish between a seminoma and a non-seminoma and, among non-seminomas, will determine histological subtype (i.e. yolk sac tumour, choriocarcinoma, embryonal cell carcinoma or teratoma). Tumour markers aid in diagnosis (e.g. elevated AFP is consistent with a non-seminoma or a mixed seminoma/non-seminoma) and are used to determine prognosis and direct decisions on postoperative treatment.
**Staging and risk categories**

Staging of testicular cancer involves degree of spread within the scrotum and surrounding tissues, absence/presence and extent of retroperitoneal involvement, pulmonary metastases, other visceral metastases, and levels of biomarkers including β-hCG, AFP and LDH.

**Testing**

Postoperative evaluation of patients with testicular cancer should include contrast-enhanced abdominal/pelvic computerized tomography (CT) and repeat tumour markers (AFP and β-hCG). A chest CT should be obtained if an abnormality on the original chest X-ray or abdominal/pelvic CT is reported. Other pretreatment laboratory tests, including complete blood count and tests of renal and hepatic function, should also be ordered. Where available, some clinicians obtain baseline pulmonary function tests, including diffusion capacity testing, before initiation of bleomycin. Imaging of the brain is recommended only in the setting of neurological signs or symptoms.

**Administration and care of patients**

The medical management of testicular cancer is based on pathology (seminoma versus non-seminoma), disease stage and the status of the tumour as defined by tumour markers, and sites of disease. Postoperative chemotherapy is administered to men at risk for disease recurrence, with longer-course treatment for those with higher-risk disease. Administration of chemotherapy requires intravenous infusion capacity, and regular and ready patient access to clinical care. Chemotherapy is typically given in an outpatient facility, although inpatient admission is sometimes required to control the side-effects of chemotherapy or for close monitoring of seriously ill patients with advanced disease. Intravenous hydration and close laboratory monitoring are requirements with cisplatin administration in order to prevent nephrotoxicity. Careful monitoring by history and physical examination for bleomycin toxicity (e.g. new pulmonary symptoms, basilar rales or pulmonary restriction) is essential, with early discontinuation if signs, symptoms or altered pulmonary function develop (17). Prophylactic antiemetics are essential, since cisplatin is highly emetogenic.

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 nephrotoxicity, bone marrow suppression, infection, gastrointestinal toxicity and pulmonary toxicity. Serum markers should be obtained with each course of chemotherapy to monitor for appropriate treatment response. The half-life of β-hCG is 1.5 days and that of AFP 5 days; prolonged half-lives of these markers during chemotherapy predict increased risk of recurrence and adverse prognosis.
Overview of regimens

Standard regimens for stage II and III seminoma or non-seminoma – good risk patients

- **BEP (adult)** – 21-day cycle, 3 cycles
  - bleomycin 30 units IV bolus on days 1, 8 and 15
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

- **BEP (prepubertal children)** – 21-day cycle, 3 cycles
  - bleomycin 15 units/m² IV bolus on day 1 (maximum dose 30 units)
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin¹ 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

Alternative regimen

- **EP (adult)** – 21-day cycle, 4 cycles
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

Standard regimens for stage IIIB or IV, intermediate-risk seminoma or intermediate- or poor-risk nonseminoma

- **BEP (adult)** – 21-day cycle, 4 cycles
  - bleomycin 30 units IV bolus on days 1, 8 and 15
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

- **BEP (prepubertal children)** – 21-day cycle, 4 cycles
  - bleomycin 15 units/m² IV bolus on day 1; (maximum dose 30 units)
  - etoposide 100 mg/m² per day IV infused over 30 minutes on days 1–5
  - cisplatin 20 mg/m² per day IV infused over 15–30 minutes on days 1–5

Alternative regimens for patients unable to tolerate bleomycin

- **VIP (adult)** – 21-day cycle, 4 cycles
  - etoposide (VP-16) 75 mg/m² per day IV on days 1–5
  - ifosfamide² 1.2 g/m² per day IV on days 1–5
  - cisplatin 20 mg/m² per day IV on days 1–5

VIP has similar efficacy to BEP but is associated with greater haematological toxicity. BEP is therefore considered the standard of care for most patients, except those with pre-existing lung disease.

¹ For BEP in prepubertal children, an accepted substitution for cisplatin is carboplatin with a dose of AUC 7.9. This has less renal toxicity.

² Administration of ifosfamide requires the accompanying drug, mesna.
Standard regimen – salvage regimen (previously treated patients)

- **VeIP (adult)** – 21 day cycle, 4 cycles
  - vinblastine 0.11 mg/kg per day IV on days 1–2
  - ifosfamide 1.2 g/m² per day IV on days 1–5
  - cisplatin 20 mg/m² per day IV on days 1–5

Review of benefits and harms

**Benefits**

Both testicular and extragonadal germ cell tumours have the potential to be very aggressive. Without treatment, patients who develop these malignancies cannot survive, and both surgical resection of primary lesions and chemotherapy for more advanced disease are therefore extremely important. The most important improvement in the treatment of this disease was the discovery of cisplatin in the 1970s, and the observation of responses in patients with testicular tumours (4). Since that time, various regimens and treatment schedules incorporating this drug have been used with significant improvements in response rates and overall survival. In combination with orchietomy, these treatments produce an overall survival rate that approaches 100% for clinical stage I disease. Stage II disease has a cure rate of >95%, and even patients with advanced disease have overall survival rates that far exceed those in almost any other type of cancer. For patients with stage III disease, the prognosis is good, albeit dependent on stratification to good-, intermediate- and poor-risk categories (14).

The efficacy of BEP and VIP chemotherapy regimens for treatment of testicular cancer has been demonstrated in numerous phase III randomized trials. For patients with low-risk stage III disease, treatment with three cycles of BEP or four cycles of cisplatin plus etoposide is associated with favourable outcomes, with cure rates and overall survival often in excess of 90% (5, 6, 8, 10). Patients with intermediate-risk stage III disease have achieved progression-free survival of 60–80% with four cycles of BEP or VIP and overall survival of 70–90% (12, 13, 18). In high-risk stage III patients, durable responses are of the order of 60%, with overall survival rates mostly above 50% two years after the start of treatment (12, 19-22) and the majority of late relapses occurring after more than five years (23). The role of chemotherapy in this disease is thus of paramount importance.

BEP and VIP regimens were compared in an analysis of an intergroup trial of 283 patients with advanced germ cell tumours (13). After a median follow-up of 7.3 years, rates of overall and progression-free survival were comparable for the two regimens; however, greater toxicity – primarily haematological – was observed in the VIP arm.

In relapsed disease, standard-dose therapy with cisplatin, combined with two drugs not received by the patient in the first-line regimen, is indicated. Depending on the composition of first-line therapy, salvage treatment with vinblastine, ifosfamide and cisplatin (VeIP) or VIP has shown efficacy and these regimens are commonly used (14, 24, 25).
**Harms and toxicity considerations**

**Common**

Common toxicities associated with treatment include myelosuppression, coronary artery disease, hypogonadism and decreased spermatogenesis, occasionally leading to infertility. Men treated with cisplatin commonly experience peripheral neuropathy, tinnitus and some degree of hearing loss (26). With regard to risks during surgery, common issues would include wound infection and intra-operative surgical complications.

The most important toxicities to consider with standard chemotherapy regimens for germ cell tumours are marrow suppression, neutropenic fever, cisplatin-induced nephrotoxicity and bleomycin-induced pulmonary toxicity. With cisplatin, close monitoring of routine laboratory tests and aggressive intravenous hydration before and after chemotherapy are necessary to avoid significant decline in renal function. With prophylactic hydration, reductions in glomerular filtration rate occurs in 20–30% of patients on cisplatin (26).

**Serious**

It has been shown that 9 weeks (3 cycles) of bleomycin is essentially devoid of any clinically significant pulmonary toxicity (6, 7, 27, 28). However, the risk of toxicity is dose-dependent (increasing with cumulative doses above 450 units) (26), and patients should be closely monitored for cough, dyspnoea, fever, lung restriction, hypoxia or rales, which can be signs and symptoms 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. Risk factors for bleomycin lung toxicity are underlying lung disease, age over 50 years, renal dysfunction and smoking, and consideration of alternative therapies is often indicated.

There is a small but significant increase in the risk for secondary solid cancers that are typically diagnosed years after completion of treatment. Testicular cancer survivors, particularly those who received cumulative etoposide doses of more than 2000 mg/m² contained in the VIP regimen, are also at risk for myelodysplastic syndrome or acute leukaemia (27-31).

One adverse event that is more specific to patients who undergo RPLND is retrograde ejaculation, which can be reduced if the procedure is performed with a nerve-sparing surgical approach (4). Sperm banking is indicated before chemotherapy, radiation therapy for seminoma and RPLND.

**Recommendations**

The Expert Committee noted the available evidence demonstrating high cure rates associated with the proposed chemotherapy regimens for testicular 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. The Committee
also recommended that bleomycin, etoposide, ifosfamide and vinblastine be included on both Model Lists for this indication. 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.

Inclusion of G-CSF on the EML was considered by the Expert Committee in a separate application.


