TESTICULAR GERM CELL TUMORS

Executive Summary

Testicular germ cell tumors account for approximately 1% of all newly diagnosed male cancers worldwide, and in 2012, there was estimated to be over 10,000 deaths from this disease [1]. It is the most commonly diagnosed malignancy in men aged 15-40 in developed countries [2], and thus improved outcomes are important both medically and economically because of the number of productive life-years lost. The incidence of testicular cancer in low to middle income countries (LMC) is about 20% of that observed in more developed countries, with a cumulative lifetime risk similar to that of Hodgkin lymphoma, melanoma, and multiple myeloma respectively[3]. Testicular cancer is most commonly seen in young men but can also be seen in pediatric patients and the benefits of therapy are similar in the 2 age groups (regimen distinctions are included in the present briefing).

Testicular germ cell tumors are divided into two groups, seminomas and non-seminomas, with non-seminomas being subdivided further into 4 distinct histologies (yolk sac tumor, choriocarcinoma, embryonal cell carcinoma, and teratoma). Approximately 90% of germ cell tumors arise in the testicles, though extragonadal primary tumors of the retroperitoneum, mediastinum, and pineal gland do occur. While most extragonadal tumors are more challenging to treat, in general, germ cell tumors have an excellent overall prognosis with 5-year survival rates of >95% in developed countries.

Cure rates for clinical stage I tumors 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 vs RT for seminoma and RPLND for non-seminoma vs short course chemotherapy. If these options (including aggressive marker/ radiographic surveillance) are not expected to be available to men from LMCs, an option would short course post operative chemotherapy (i.e., carboplatin x1-2 for seminoma and BEP x1 for non-seminoma.

In addition to radical inguinal orchiectomy, the backbone of standard therapy includes cisplatin-based combination chemotherapy, most often bleomycin, etoposide, and cisplatin (BEP). The duration of treatment is based upon stratification of advanced disease patients into three risk groups: good risk, intermediate risk, and poor risk based on pathology, degree of tumor marker elevation (alpha-fetoprotein and beta-human chorionic gonadotropin), LDH and imaging. In good risk disease, either three cycles of BEP or a combination of etoposide and cisplatin (EP) for four cycles 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 (VePesid), ifosfamide, and cisplatin (VIP) which has shown similar efficacy but with increased hematologic 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 tumor markers as this may represent teratoma which is not chemo-sensitive or residual viable cancer. This surgery is not recommended outside specialized centers of excellence with high volumes, not typically seen in most LMCs. With the combination of the above therapies, patients with advanced disease exhibit approximate cure rates of >90% for good risk, 75% for intermediate risk, and 50% for poor risk status [14].

It is also important to note that direct comparisons of platinum agents have consistently demonstrated inferior outcomes with the substitution of carboplatin for cisplatin, and therefore, it is strongly recommended that cisplatin be used for the treatment of germ cell tumors [15-16]. Carboplatin has been compared to cisplatin (not currently in the WHO model, History of Essential Medicines 2013) and found to be inferior in two randomized trials with 10-19% higher relapse rate and decrease in relapse-free survival [15-17]. Based on these findings, we recommend the addition of cisplatin to the WHO’s Essential Medicines List.

Public Health Relevance

Testicular germ cell tumors account for 1% of all newly diagnosed male cancers worldwide and are the most commonly found cancer in young males ages 20 to 40 [25]. Epidemiological information concerning germ cell tumors 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. GLOBOCAN estimated the worldwide incidence of testicular cancer in 2012 to be 55,266 (ASR of 1.5 per 100,000) [26]. Incidence in more developed regions in 2012 was 32,470 (ASR of 5.4 per 100,000) and incidence rate in 2012 in less developed regions was 22,256 (ASR of 0.8 per 100,000). According to GLOBOCAN, highest incidence rates in 2012 were in the European region (23,560 cases with an ASR of 5.4 per 100,000) and in the Americas region (16,162 with an ASR of 3.4 per 100,000). This is in accordance with recent studies indicating an increasing rate of germ cell tumors in the Western world over the last several decades [27].

GLOCOBAN approximates global mortality rate due to testicular cancer in 2012 to be 10,351 (ASR of 0.3 per 100,000). Mortality rates in more developed regions (2209 with an ASR of 0.4 per 100,000) and less developed regions (8142 with an ASR of 0.3 per 100,000) are comparable. Highest mortality rates were found to be in the East Mediterranean region (1438 with an ASR of 0.5 per 100,000) and European regions (1988 with an ASR of 0.5 per 100,000).

Requirements for diagnosis, treatment, and monitoring

Diagnostics: Initial evaluation of a suspicious testicular mass should include a complete history and physical exam, tumor markers-including alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG), LDH, chemistries, a chest x-ray, and testicular ultrasound. Transcrotal illumination may differentiate solid masses from hydroceles, but cannot be used to rule out cancer as 20% of testicular cancer patients have associated hydroceles. If a hypo-echoic testicular mass is found on ultrasound, radical inguinal orchiectomy is recommended for
treatment as approximately 95% of these lesions are malignant [4]. Scrotal biopsy is not advised as most masses are malignant, and biopsy can result in seeding of the biopsy tract with malignant cells. Pathology will distinguish between a seminoma and a non-seminoma and, among non-seminomas, will determine histologic subtype (i.e., yolk sac tumor, choriocarcinoma, embryonal cell carcinoma, or teratoma). Tumor markers aid in diagnosis (i.e., an elevated AFP is consistent with a non-seminoma or a mixed seminoma/non-seminoma) and are used to determine prognosis and to direct postoperative treatment decision-making.

Staging and Risk Categories: Staging of testicular cancer involves degree of spread within the scrotum and surrounding tissues, absence or presence (and extent) of retroperitoneal involvement, pulmonary metastases, other visceral metastases, and levels of biomarkers including HCG, AFP, and LDH. The details of these staging categories can be found in reference

Testing: Postoperative evaluation of men with testicular cancer should include contrast enhanced abdominal/pelvic computed tomography (CT) and repeat tumor markers (AFP and β-HCG). A chest CT should be obtained if there is an abnormality reported on the original chest x-ray or abdominal/pelvic CT. Other pre-treatment 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 (PFTs), including diffusion capacity testing (DLCO), prior to bleomycin initiation. Imaging of the brain is only recommended in the setting of neurologic signs or symptoms.

Administration and Care of Patients: The medical management of testicular cancer patients is based on pathology (seminoma versus non-seminoma), disease stage, and the status of the tumor as defined by tumor markers, LDH, and sites of disease. Postoperative chemotherapy is administered to men at risk for disease recurrence, with longer course treatment administered to those with higher risk disease, as outlined below. Chemotherapy administration requires intravenous infusion capacity, and regular and ready access to clinical care. Chemotherapy is typically given in an outpatient facility, though sometimes inpatient admission is required to control side effects from chemotherapy or when close monitoring is required in seriously ill patients with advanced disease. Intravenous (IV) hydration and close laboratory monitoring are requirements with cisplatin administration in order to prevent nephrotoxicity. Careful monitoring by history and physical exam for bleomycin toxicity (i.e., new pulmonary symptoms, basilar rales, or pulmonary restriction) , with early discontinuation if signs, symptoms or altered pulmonary function testing arise [23]. Prophylactic IV anti-emetics are essential , given that 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. During treatment with chemotherapy, serum markers should be obtained with each course of therapy to monitor for appropriate treatment response. The half-life of hCG is 1.5 days and that of AFP is 5 days. Prolonged half-lives of these markers during chemotherapy predict increased risk of recurrence and adverse prognosis.
Overview of Regimens

**Stage II and III Seminoma or Nonseminoma – Good Risk Patients**

**BEP (ADULT)**
Bleomycin 30 IU/IV bolus on days 1, 8, and 15
Etoposide 100mg/m2/d IV infused over 30 minutes on days 1-5
Cisplatin 20mg/m2/d IV infused over 15-30 minutes on days 1-5
- Repeat cycle every 21 days for **three** cycles

**BEP (PREPUBERTAL CHILDREN)**
Bleomycin 15 U/m2 on day 1; maximum dose 30U
Etoposide 100mg/m2/d IV infused over 30 minutes on days 1-5
Cisplatin* 20mg/m2/d IV infused over 15-30 minutes on days 1-5
- Repeat cycle every 21 days for **three** cycles
- *For BEP, an accepted substitution for cisplatin among **prepubertal children** is carboplatin with a dose of AUC 7.9. This has less renal toxicity.

**OR,** for **adults only**

**EP (ADULT)**
Etoposide 100mg/m2/d IV over 30 minutes on days 1-5
Cisplatin 20mg/m2/d IV over 15-30 minutes on days 1-5
- Repeat cycle every 21 days for **four** cycles

**Stage IIIIB or IV, Intermediate Risk Seminoma or Intermediate or Poor Risk Non-seminoma**

**BEP (ADULT)**
Bleomycin 30 IU/d IV bolus d1, 8, and 15
Etoposide 100mg/m2/d IV infused over 30 minutes on days 1-5
Cisplatin 20mg/m2/d IV infused over 15-30 minutes on days 1-5
- Repeat cycle every 21 days for **4** cycles

**BEP (PREPUBERTAL CHILDREN)**
Bleomycin 15 U/m2 on day 1; maximum dose 30U
Etoposide 100mg/m2/d IV infused over 30 minutes on days 1-5
Cisplatin* 20mg/m2/d IV infused over 15-30 minutes on days 1-5
- Repeat cycle every 21 days for **4** cycles
- *For BEP, an accepted substitution for cisplatin among **prepubertal children** is carboplatin with a dose of AUC 7.9. This has less renal toxicity.

**OR,** for **adults** who may not tolerate bleomycin, VIP, below:
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**VIP***(ADULT)***
Etoposide (VP-16) 75mg/m2/d IV on days 1-5
Ifosfamide 1.2g/m2/d IV on days 1-5
Cisplatin 20mg/m2/d IV on days 1-5
Mesna 400mg IV bolus prior to the first ifosfamide dose, then 1.2g/m2/d IV infused continuously on days 1-5
- Repeat cycle every 21 days for 4 cycles

**VIP regimen has similar efficacy to BEP but with more hematologic toxicity, therefore, BEP is considered the standard of care for most patients, except in those patients with pre-existing lung disease.**

**Review of Benefits and Harms**

**Benefits**
Both testicular and extragonadal germ cell tumors have the potential to be very aggressive. Without treatment, patients who develop these malignancies cannot survive, and therefore, both surgical resection of primary lesions and chemotherapy for more advanced disease are extremely important. The most important improvement in the treatment of this disease was the discovery of cisplatin in the 1970s. 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 orchiectomy, these treatments produce an overall survival rate which 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 which far exceed almost any other type of cancer [4]. For patients with stage III disease, the prognosis is dependent on stratification to good, intermediate, and poor risk categories with cure rates of >90%, 75%, and 50% respectively [14]. Therefore, the role of chemotherapy in this disease is immensely important. Furthermore, given the relatively young age at diagnosis, the potential for a significant improvement in the number of productive life-years gained is another clear benefit.

**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.[24] With regards to risks during surgery, common issues would include wound infection and intra-operative surgical complications.

The most important toxicities to consider from standard chemotherapy regimens for germ cell tumors are marrow suppression, neutropenic fever, cisplatin-induced nephrotoxicity and bleomycin-induced pulmonary toxicity. With cisplatin, close monitoring of routine labs and aggressive IV hydration pre and post-chemotherapy are necessary to avoid significant declines in
renal function. With prophylactic hydration, reductions in GFR occurs in 20-30% of patients on cisplatin.[24]

**Serious**

In regards to bleomycin toxicity, it has been shown that 9 weeks (3 cycles) of bleomycin is essentially devoid of any clinically significant pulmonary toxicity.[6,7,18] However, the risk of toxicity is dose-dependent (increasing with cumulative doses above 450 units) [24], and patients should be closely monitored at each visit for cough, dyspnea, fever, lung restriction, hypoxia, or rales that 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 > 50 yo, renal dysfunction, and smoking and considerations for alternative therapies are often indicated.

There is a small (incidence <0.5%), but significant increase in the risk for secondary solid cancers that are typically diagnosed years beyond completion of treatment. Testicular cancer survivors are also at risk for myelodysplastic syndrome or acute leukemia [18-22,24], particularly among those receiving cumulative etoposide doses of more than 2,000mg/m2 contained in the VIP regimen.[22]

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

**Systematic reviews**


**Recommendations**

The reviewers recommend the incorporation of testicular 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


