Testicular Cancer: II

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Cover Illustration by Roy Scott
I. INTRODUCTION

This is the second of a 2-part manual on testicular cancer. The second part discusses treatment of good-prognosis advanced stage disease and of poor-prognosis germ cell tumors (GCTs), management of residual masses, salvage chemotherapy, toxicities of treatment, and mediastinal GCTs. The first part discussed epidemiology, biology, diagnosis, and staging of GCTs in general as well as treatment of early stage seminomatous and nonseminomatous GCTs. Both parts contain sample board review questions and answers for self-assessment. The first part was published as “Testicular Cancer: I” in the Hospital Physician Oncology Board Review Manual, Volume 6, Part 3.

II. TREATMENT OF GOOD-PROGNOSIS ADVANCED STAGE DISEASE

A. Overview. The development of highly effective chemotherapy for advanced stage GCTs represents one of the greatest success stories of modern oncology. Advanced stage disease includes bulky stage II (IIC) and stage III disease. Roughly 70% to 80% of these patients can now be cured with chemotherapy and, if necessary, surgery. As regimens were being tested in the 1970s and 1980s, it became clear that some advanced stage patients had a much better prognosis than others; therefore, subsequent trials were tailored to either good- or poor-risk patients. With more than 90% of good-risk patients achieving long-term disease-free survival, attention shifted to minimizing treatment-related toxicity in this population, although more effective treatments were sought for poorer risk patients. At this time, 2 standard regimens are used for patients with good-risk GCTs: 3 cycles of bleomycin, etoposide, cisplatin (BEP) or 4 cycles of etoposide and cisplatin (EP) (Table 1).

B. Early trials. In early trials, treatment with 4 cycles of cisplatin, vinblastine, and bleomycin (PVB) was the first regimen shown to cure most patients with metastatic or bulky retroperitoneal disease. Subsequently, a multicenter, randomized trial demonstrated that 4 cycles of BEP (which substitutes etoposide for vinblastine) produced equivalent results as PVB with less toxicity. Moreover, in patients with bulkier disease, BEP resulted in higher survival. This trial established 4 cycles of BEP as the standard regimen for advanced stage GCTs. Attempts to reduce toxicity in good-risk
patients by replacing cisplatin with carboplatin resulted in a higher relapse rate, and this strategy has been abandoned. Carboplatin does play a role in high-dose chemotherapy (see Sections III.F. and V.C.) and has shown promise as adjuvant chemotherapy in clinical stage I seminomas.

C. **Three cycles of BEP chemotherapy.** Treatment strategies evolved from early trials, with 3 cycles of BEP chemotherapy becoming the mainstay. In 1989, a multicenter randomized trial comparing 3 versus 4 cycles of BEP in good-risk patients reported that both arms achieved an overall disease-free survival of 92%, although toxicity was significantly reduced in those receiving only 3 cycles of chemotherapy.\(^3\) Thus, 3 cycles of BEP became the standard treatment for good-risk GCTs. A long-term follow-up analysis of a subgroup of the patients within this study confirmed that there was no significant survival difference between the 2 arms when median follow-up was more than 10 years.\(^4\)

D. **Eliminating bleomycin.** Attempts were made to eliminate bleomycin, which can result in severe, sometimes fatal, pulmonary fibrosis (bleomycin lung) and in Raynaud’s phenomenon. Some trials have reported a 1% to 2% fatality rate attributable to bleomycin lung. Thus, numerous efforts have been made to eliminate bleomycin from chemotherapy regimens for good-risk patients with disseminated GCTs. Unfortunately, none of these trials has clearly established that bleomycin can be eliminated from BEP without compromising efficacy.

1. **Three cycles of VAB-6 versus 4 cycles of EP.**
   The efficacy of other regimens, such as EP alone, has also been compared with traditional treatments. Of several trials addressing this issue, only one has demonstrated acceptable results with EP alone. This single-institute trial at Memorial Sloan Kettering Cancer Center assessed 4 cycles of EP compared with 3 cycles of VAB-6 (vinblastine, cyclophosphamide, dactinomycin, bleomycin, and cisplatin).\(^5\) VAB-6 is thought to be a BEP equivalent, although BEP and VAB-6 have never been directly compared. With 82 patients in each arm, no significant difference was seen between the 2 arms in the achievement of a disease-free state or in relapse or survival. Despite its limitations, many experts in testicular cancer believe this trial established that 4 cycles of EP are an acceptable alternative to 3 cycles of BEP. All major treatment guidelines state that 4 cycles of EP are equivalent to 3 cycles of BEP.\(^6\) A 4-cycle EP regimen is thus part of standard care in 2001 even though it has never been shown to be equivalent to 3 cycles of BEP in a head-to-head trial.

2. **Four cycles of BE\(_{900}\)P versus 4 cycles of E\(_{900}\)P.**
   A subsequent European trial assessed 4 cycles of BE\(_{900}\)P compared with 4 cycles of E\(_{900}\)P (the subscript refers to the fact that this study used a lower dose of etoposide: 360 mg/m\(^2\) body surface area/cycle instead of the US dose of 500 mg/m\(^2\)/cycle).\(^7\) The BE\(_{900}\)P produced a higher complete response rate (95% versus 87%, \(P = 0.0075\)), but no significant differences were found in treatment failure, time to progression, and overall survival (all of which favored the bleomycin arm). This trial does not support eliminating bleomycin from BE\(_{900}\)P, but its results cannot be extrapolated to US doses of BEP and EP.

3. **Three cycles of BEP versus 3 cycles of EP.**
   A multicenter US trial assessed 3 cycles of BEP compared with 3 cycles of EP (using etoposide at 500 mg/m\(^2\)/cycle) in good-risk patients.\(^8\) This trial found that BEP produced better overall survival (95% versus 86%, \(P = 0.01\)). Therefore, 3 cycles of EP is not considered adequate therapy for metastatic testicular cancer.

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**Table 1. Standard Chemotherapy Regimens for Testicular Cancer**

<table>
<thead>
<tr>
<th>First-line therapy</th>
<th>Cycles, n</th>
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<tbody>
<tr>
<td>BEP (3 or 4*)</td>
<td></td>
</tr>
<tr>
<td>EP (only for good-risk disease)</td>
<td>4†</td>
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</tbody>
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**Salvage therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cycles</th>
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<tbody>
<tr>
<td>VIP</td>
<td>4</td>
</tr>
<tr>
<td>VeIP</td>
<td>4</td>
</tr>
<tr>
<td>High-dose chemotherapy with autologous stem-cell rescue</td>
<td></td>
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</tbody>
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BEP = bleomycin, etoposide, and cisplatin; EP = etoposide and cisplatin; VeIP = vinblastine, ifosfamide, and cisplatin; VIP = etoposide, ifosfamide, and cisplatin.

*Depending on whether the patient has good-risk or poor-risk disease.
†Eliminates problems with bleomycin toxicity (i.e., pulmonary fibrosis, Raynaud’s phenomenon).
IV. TREATMENT OF POOR-PROGNOSIS GERM CELL TUMORS

A. Overview. Patients with nonseminomatous GCTs (NSGCTs) who have a poor prognosis include those with highly increased marker levels (ie, β–human chorionic gonadotropin [β-hCG], α-fetoprotein [AFP], or lactate dehydrogenase [LDH]), nonpulmonary visceral metastases, or mediastinal primary tumors. The therapeutic response for these patients has been less than satisfactory; the 5-year survival rate of patients with intermediate and poor-prognosis is approximately 80% and 50%, respectively. Therefore, trials for intermediate- and poor-prognosis patients have focused on improving cure rates, whereas trials for good-prognosis patients have focused on reducing treatment-related toxicity. Standard first-line therapy remains 4 cycles of BEP (Table 1). However, early evidence suggests that high-dose chemotherapy may produce better results in some patients.

B. Four cycles of BEP chemotherapy. As previously discussed, a 1987 randomized trial reported that 4 cycles of BEP produced superior results when compared with 4 cycles of PVB in patients with advanced-stage GCTs who had high tumor volume. In these poor-prognosis patients, BEP was associated with a better response rate and longer survival. Unfortunately, this trial only had a median follow-up of less than 2 years and long-term results have never been published. To this day, 4 cycles of BEP remains the standard of care.

C. VIP versus BEP. In the 1980s and early 1990s, ifosfamide became a key element of chemotherapy regimens for patients with relapsed GCTs. Combining ifosfamide with cisplatin and either vinblastine (VeIP) or etoposide (VIP) resulted in successful salvage rates of approximately 25% in patients who had previously received platinum-based chemotherapy. These results led to a multicenter, randomized trial in which 286 patients with advanced metastatic GCTs were treated with 4 cycles of either VIP or BEP. Response rates, failure-free survival, and overall survival were all similar for the 2 regimens; however, VIP resulted in greater hematologic and genitourinary toxicity. Four cycles of BEP thus remained the standard first-line regimen.

D. Alternating chemotherapy regimens. An early strategy to improve outcomes for patients with poor-prognosis GCTs was the use of either sequential or alternating non–cross-resistant chemotherapy regimens. These regimens remain experimental. Two of them, POMB/ACE (cisplatin, vincristine, methotrexate, and bleomycin alternating with dactinomycin, cyclophosphamide, and etoposide) and CISCA VB (cisplatin, cyclophosphamide, and doxorubicin alternating with vinblastine and bleomycin) have produced promising results.
Data assessing CISCA VB compared with BEP in a randomized trial are eagerly awaited. A similar approach has involved intensification of initial cisplatin dose delivery by using less myelotoxic regimens with a shorter interval between cycles and following up with one of the standard regimens. This approach was studied in a phase III trial using BEP as the control; BEP was better tolerated and produced equivalent results. More recent trials of dose intensification have reported 3-year progression-free survival as high as 81%, and multi-institutional phase II trials are underway.

E. Escalating the dose of cisplatin. A 1991 trial randomly assigned patients with poor-risk GCTs either (1) to a standard US dose of BEP or (2) to BEP with a double dose of cisplatin. The higher dose of cisplatin caused more toxicity but did not result in either a higher response rate or longer survival.

F. High-dose chemotherapy with autologous stem-cell rescue (autologous bone marrow transplant). In recent reports, high-dose chemotherapy with autologous stem-cell rescue (auto–bone marrow transplantation [auto-BMT]) has produced promising results as first-line therapy in poor-prognosis patients. Most current regimens include a combination of etoposide, carboplatin, or cisplatin, and either cyclophosphamide or ifosfamide. Initial protocols involved bone-marrow harvest, but most current trials use plasmapheresis to collect circulating stem cells after induction chemotherapy. First-line auto-BMT remains experimental, but a randomized trial comparing this approach to 4 cycles of BEP is nearing completion. The only published randomized trial showed no benefit to auto-BMT, but this early study had several severe limitations. A subsequent retrospective multivariate and matched-pair analysis suggested that progression-free survival (75% versus 59%, P = 0.0056) and overall survival (82% versus 71%, P = 0.0184) were significantly prolonged using first-line auto-BMT when compared with standard therapy using either BEP or VIP. Treatment-associated fatality is less than 5%. Further attempts to avoid toxicity have included limiting first-line auto-BMTs to those patients whose serum tumor markers fail to decrease as expected (based on their biologic half-life) during the first 2 cycles of induction chemotherapy.

IV. MANAGEMENT OF RESIDUAL MASSES

A. Seminomas
1. Overview. Management of residual masses after chemotherapy in patients with pure seminoma varies among different institutions. Most patients with seminomas have residual masses after chemotherapy, but fewer than 1 in 4 of those with masses have residual malignancy. Furthermore, chemotherapy provokes a scirrhous or desmoplastic reaction in seminomas that renders retroperitoneal lymph node dissection (RPLND) and resection of residual masses technically difficult and often impossible. Residual masses often adhere to the inferior vena cava and abdominal aorta, and tissue planes are obliterated. Surgery in this setting is thus generally unnecessary, and complete resection is often unfeasible. When attempted, the operation may be limited to biopsy of residual masses to determine whether radiation and/or additional chemotherapy are indicated.

2. Which masses require additional treatment? Retrospective studies have attempted to identify which patients with residual masses may benefit from additional treatment; these studies have identified the size of the residual mass as strongly predictive of the presence of viable malignancy. Patients with residual masses smaller than 3 cm in diameter only rarely relapse, and their masses almost always consist solely of necrosis and fibrosis; they can be observed without additional therapy. Patients with residual masses greater than 3 cm in diameter have 3 options: surgery, radiation, or surveillance. No consensus exists on which option is best or even on the 3-cm cutoff. However, there is little evidence that radiation therapy is beneficial if residual seminoma has not been proven by biopsy.

B. Nonseminomatous germ cell tumors (NSGCT)
1. Overview. The management of residual masses after chemotherapy in patients with NSGCTs remains controversial. NSGCTs differ from pure seminomas in several important respects, and mixed GCTs with seminomatous elements are treated as NSGCTs. First, most patients have a complete response to chemotherapy alone and only about 10% of those...
with residual masses have viable cancer found at surgery. Second, resection of residual masses in NSGCTs does not present the same technical challenges or operative risks as seminomas; complete resection is often possible. Third, because NSGCTs may contain teratomatous elements (which are not generally chemosensitive), surgery may be necessary to achieve a cure, regardless of whether additional chemotherapy is administered. Finally, radiation therapy does not play a role in managing NSGCTs because the tumors are not radiosensitive.

2. **Patients with persistently increased serum tumor markers.** NSGCT patients with residual masses are generally only candidates for RPLND if their serum tumor markers are normal at the end of chemotherapy. Those with persistently increased tumor markers should receive salvage chemotherapy in almost all circumstances. One rare exception is that patients who present with highly increased β-hCG may have a persistent, stable, mild elevation of this marker in the absence of residual tumor. Unless the β-hCG level starts to increase, these patients generally do not require additional chemotherapy. Similarly, an increased or rising AFP at the end of chemotherapy can reflect drug-induced hepatic toxicity. Following markers over time can be useful in these cases because markers usually increase in the presence of residual disease. An important point to emphasize is that persistent elevation of tumor markers in the absence of residual disease is not considered typical.

3. **Patients with normalized serum tumor markers.** Recommendations vary regarding patients with normal tumor markers and persistent masses. Attempts to risk stratify these patients have identified the size of the residual mass, the degree of radiographic response to chemotherapy, and the presence of teratoma in the primary tumor as predictors of the presence of viable cancer or teratoma in residual masses. However, no criteria have been identified that reliably exclude malignancy or teratoma; thus, determining which masses can be safely observed has not been made clear. Some level of agreement has been reached that resection of residual masses is clearly indicated in the following circumstances: masses that are greater than 2 cm in diameter; masses that have not shrunk by at least 90%; and all masses in patients with teratomatous elements in their primary tumor. The most conservative approach is to resect all residual masses in patients with NSGCTs.

4. **Treatment after resection of residual masses.** Patients undergoing resection who are found to have only teratoma or fibrosis/necrosis need no additional treatment. However, patients found to have viable cancer generally receive 2 additional cycles of chemotherapy (typically the same chemotherapeutic regimen as used initially).

## V. SALVAGE CHEMOTHERAPY

### A. Overview

Most patients with disseminated GCTs achieve a disease-free state after induction chemotherapy either with or without resection of residual masses. Those who do not achieve a disease-free state and those who relapse are treated with salvage chemotherapy (Table 1). Overall, approximately 25% of patients receiving salvage chemotherapy achieve durable remissions; however, approximately 50% of patients with pure seminoma achieve remission. Patients who achieve a complete remission and then relapse have a distinctly better prognosis than do those who either fail to achieve a complete remission or those who relapse within 1 month of receiving cisplatin. Patients who relapse after a complete remission lasting more than 2 years, however, tend to have chemotherapy-resistant disease and are rarely cured unless they have surgically resectable disease. Those who progress while receiving BEP or other cisplatin-based chemotherapy have a particularly poor prognosis. Patients with primary NSGCTs of the mediastinum who either relapse or fail to respond to induction chemotherapy almost always die of their disease. Because of disappointing results with standard salvage regimens, high-dose chemotherapy is playing an increasingly greater role in treating refractory and relapsing disease.

### B. Standard-dose salvage chemotherapy

The 2 standard salvage regimens combine VeIP or VIP. Between 33% and 50% of patients treated with these regimens achieve a complete remission, and 20% to 30% will be cured. Among patients with pure seminomas, approximately 50% will be cured.
surprisingly, trials that exclude patients who progress while receiving cisplatin-based chemotherapy produce more favorable results. Myelosuppression is severe with these regimens, and most patients develop febrile neutropenia.

C. **High-dose chemotherapy with autologous stem-cell rescue (auto-BMT).** High-dose chemotherapy has an established role as second-line salvage therapy for patients with relapsing or refractory GCTs and is becoming accepted by some as first-line salvage treatment. No randomized trials comparing standard-dose and high-dose salvage regimens have been published, but at least one trial is underway. Initial trials of high-dose chemotherapy were restricted to patients who had had multiple relapses and multiple previous courses of chemotherapy. In that setting, treatment-related mortality was as high as 20%. With greater experience and a shift toward using high-dose chemotherapy as first-line salvage, treatment-related mortality in published series has decreased to less than 5%. Meanwhile, outcomes in phase I and II trials have improved. Although VeIP and VIP successfully salvage 20% to 25% of patients with recurrent or refractory disease, high-dose chemotherapy as second-line salvage therapy produced durable remissions in 15% to 20% of the remainder. When used as initial salvage treatment, a single course of high-dose therapy produced a durable remission in about 35% of patients. More promising, recent trials of 2 cycles of high-dose therapy used as the initial salvage regimen report long-term disease-free survival ranging from 40% to 55%. Interpretation of these results, however, is complicated by the fact that the most recent trials have excluded patients with various poor-prognostic features. At least part of the improved outcomes must therefore be attributed to patient selection. Randomized trials are needed to demonstrate which salvage approach is optimal.

D. **Future directions.** For patients with recurrent or refractory mediastinal NSGCTs and for patients whose tumors are absolutely refractory to cisplatin, treatment results remain highly unsatisfactory and new approaches are needed. Paclitaxel and gemcitabine have both shown activity against cisplatin-refractory tumors, and early trials incorporating paclitaxel into salvage regimens have reported promising results.

E. **Prognostic factors for patients undergoing salvage therapy**

1. **Cisplatin resistance and response to previous therapy.** GCTs are considered cisplatin sensitive, relatively cisplatin refractory, or absolutely cisplatin refractory. Absolute cisplatin refractory GCTs progress while the patient is being treated with cisplatin-based chemotherapy. Depending on the published study, relatively cisplatin refractory GCTs are variously defined as tumors that fail to go into complete remission with cisplatin-based therapy or as tumors that have at least a partial remission but relapse within 1 month of treatment with cisplatin. The likelihood of successfully salvaging a patient declines with increasing cisplatin resistance. Among GCT patients undergoing salvage therapy, those who achieved either a complete remission or a partial remission with normal serum tumor markers when treated with initial, standard-dose chemotherapy have a better long-term prognosis than those who did not.

**VI. TOXICITIES OF TREATMENT**

A. **Pulmonary.** Bleomycin is associated with a dose-related incidence of pulmonary fibrosis that is sometimes fatal. This reaction can result in pulmonary nodules that are difficult to distinguish from metastases. No treatment has been established for this condition, and the main strategy has been to avoid it by discontinuing bleomycin when significant pulmonary toxicity is evident.
Patients who are smokers and those who have undergone previous radiation therapy to the chest appear to be at increased risk. Exposure to high levels of supplemental oxygen is thought to exacerbate bleomycin-related lung damage. Therefore, patients who have been treated with bleomycin should not receive higher levels of oxygen than necessary to maintain adequate saturation of arterial blood; this is particularly important for patients undergoing surgery. Currently, no accurate test for early bleomycin lung toxicity is available. Most oncologists depend on careful monitoring of pulmonary signs and symptoms as well as pulmonary function tests (especially carbon monoxide diffusion in the lung [DLCO]) despite the poor sensitivity and specificity of these tests for detecting bleomycin toxicity.

B. Secondary malignancies and other effects
   1. Leukemia. Etoposide can result in secondary acute myeloblastic leukemias that are highly refractory to treatment. The incidence appears to be dose-related. In patients receiving a cumulative dose of less than 2000 mg/m², the incidence is less than 0.5%. In patients receiving more than 3000 mg/m², the incidence is greater than 5%. These leukemias typically appear 2 to 4 years after treatment.
   2. Solid tumors. Patients who have received radiation therapy for seminomas show an increased incidence of gastrointestinal malignancies as well as soft-tissue sarcomas. These cancers tend to appear 10 or more years after treatment.

C. Myelosuppression. All standard GCT chemotherapy regimens are associated with at least moderate myelosuppression. Patients receiving these regimens are at risk for neutropenic fevers and acute infections. Severe thrombocytopenia can occur with any of these regimens but is particularly associated with ifosfamide and high-dose chemotherapy.

D. Infertility. All GCT patients should be encouraged to bank their sperm before undergoing chemotherapy or RPLND. These patients can have problems with fertility for 3 reasons. First, most men diagnosed with testicular cancer have low sperm counts before orchiectomy or receiving chemotherapy. However, most men with stage I testicular cancers who are undergoing surveillance have been able to father children. Second, chemotherapy results in long-term oligospermia or azoospermia in a few men as well as abnormalities of sperm morphology and motility. The risk of prolonged low sperm counts appears to be related to the total number of cycles of chemotherapy administered. Third, RPLND can result in anejaculation or retrograde ejaculation. Current surgical techniques have reduced the incidence of this complication to 5% or less when performed by an experienced surgeon.

E. Cardiac and vascular effects. Bleomycin and cisplatin can cause development of Raynaud’s phenomenon. An increased risk for myocardial infarction and other cardiovascular morbidity has been reported in testicular cancer patients treated with cisplatin, but this area remains controversial.

F. Genitourinary toxicity. Cisplatin and ifosfamide are both associated with nephrotoxicity. Ifosfamide can cause hemorrhagic cystitis; mesna is given to avoid this complication. To minimize genitourinary toxicity, patients receive vigorous intravenous hydration when receiving cisplatin or ifosfamide.

G. Neurotoxicity. In GCT patients treated with cisplatin, the major neurologic side effects are peripheral neuropathy and high-pitch hearing loss.

VII. MEDIASTINAL GERM CELL TUMORS

A. Primary GCTs of the mediastinum are not classified as testicular cancer. They most often occur in the anterior mediastinum. Seminomas of the mediastinum carry the same favorable prognosis as other seminomas. They are treated with 4 cycles of cisplatin-based chemotherapy (BEP or VIP) and/or radiation. More than 75% of affected patients are long-term survivors.

B. NSGCTs of the mediastinum carry a poor prognosis and are treated with 4 cycles of cisplatin-based chemotherapy. Any residual radiologic abnormality is resected. Only about 35% of these patients are long-term survivors. Patients with NSGCTs of the mediastinum who relapse after chemotherapy are only rarely successfully salvaged, and new treatment strategies are needed for this population. Mediastinal NSGCTs are associated with an increased incidence of fatal hematologic diseases, such as myelogenous leukemia.
BOARD REVIEW QUESTIONS

Choose the single best answer for each question.

1. A 23-year-old man has a painful, indurated, enlarged testicle. He ultimately undergoes radical orchiectomy and is diagnosed with a mixed GCT. Preorchiectomy evaluation shows a serum α-fetoprotein (AFP) level of 11,000 ng/mL; computed tomography scan reveals bulky retroperitoneal lymphadenopathy. Which of the following is the most appropriate management for this patient?
   A) Retroperitoneal lymph node dissection (RPLND)
   B) Four cycles of chemotherapy with bleomycin, etoposide, and cisplatin (BEP)
   C) Three cycles of chemotherapy with BEP
   D) Four cycles of chemotherapy with cisplatin, vinblastine, and bleomycin (PVB)
   E) Four cycles of chemotherapy with etoposide, ifosfamide, and cisplatin (VIP)

2. A man is diagnosed with a pure seminoma of the left testicle with lymphovascular invasion present in the primary tumor. Further evaluation shows retroperitoneal lymphadenopathy as well as bilateral pulmonary nodules suspicious for metastasis. Preorchiectomy measurement of lactate dehydrogenase (LDH) shows levels twice the upper limit of normal; serum levels of β-human chorionic gonadotropin (β-hCG) and AFP are both normal. Which of the following treatments is most appropriate for this patient?
   A) Four cycles of BEP
   B) Four cycles of bleomycin, etoposide, and carboplatin
   C) Three cycles of etoposide and cisplatin (EP)
   D) Three cycles of BEP
   E) Four cycles of etoposide, ifosfamide, and cisplatin (VIP)

3. A young man is undergoing evaluation of a right-sided testicular mass. Ultrasonography shows multiple hypoechoic lesions in the testicle. A radical orchiectomy is performed, and his tissue diagnosis is mixed GCT. Preorchiectomy measurement of serum β-hCG shows a level of 500 IU/L. Two weeks after orchiectomy, the serum β-hCG has decreased to 300 IU/L; preorchiectomy and postorchiectomy serum levels of AFP and LDH are normal. Staging studies show no evidence of lymphatic or visceral metastases. Which of the following treatments is most appropriate for this patient?
   A) RPLND
   B) Four cycles of EP
   C) Two cycles of BEP
   D) Four cycles of BEP
   E) Surveillance
   F) Radiation therapy

4. A patient with a disseminated, intermediate-risk GCT is being treated with BEP. He completes cycle 1 of chemotherapy without any complications. However, neutropenia is evident when laboratory studies are done before the start of cycle 2. Which of the following is the most appropriate next step?
   A) Delay treatment until his neutrophil count is greater than 1000 cells/mm³
   B) Start cycle 2 as originally scheduled with a 20% dose reduction
   C) Start cycle 2 as originally scheduled at full dose
   D) Delay treatment for 1 week, then treat with a 20% dose reduction

5. Banking of sperm should be recommended before initiation of which of the following management strategies?
   A) Surveillance
   B) RPLND
   C) Chemotherapy
   D) B and C
   E) None of the above

DETAILED ANSWERS

1. (B) Four cycles of chemotherapy with BEP. This patient has an NSGCT and a poor prognosis because his AFP level is greater than 10,000 ng/mL. Other factors that convey poor prognosis include mediastinal primary tumor, βhCG greater than 50,000 IU/L, LDH more than 10 times the upper limit of normal, and nonpulmonary visceral metastases. For patients who have disease with either intermediate or poor prognosis, first-line therapy is 4 cycles of BEP. Four cycles of VIP was compared with 4 cycles of BEP in a randomized trial. Although no differences in outcome were seen, VIP proved to be more toxic. VIP remains a good alternative for patients at high risk or with early evidence of bleomycin pulmonary toxicity.

2. (D) Three cycles of BEP. This patient has a “good-risk” testicular seminoma (i.e., he has a good prognosis). All
seminomas are classified as having a good prognosis unless nonpulmonary visceral metastases are present. Tumor markers do not affect the classification of seminomas. Good-prognosis GCTs are treated with either 3 cycles of BEP or 4 cycles of EP. When compared with 3 cycles of BEP, 3 cycles of EP was found to result in shorter survival. Carboplatin has no role at this time in the treatment of good-risk GCTs because it has been shown repeatedly to be inferior to cisplatin at standard doses. VIP has not been studied as first-line treatment in good-risk patients.

3. (B) Four cycles of EP. This patient appears to have persistently increased \( \beta \)-hCG levels after orchiectomy, although the tumor markers should be checked again to confirm the finding. The serum half-life of \( \beta \)-hCG is roughly 24 hours. Therefore, this patient’s \( \beta \)-hCG levels have not decreased as much as would have predicted (using the half-life) if all the cancer had been contained in the testicle. Patients with increased tumor markers after orchiectomy who undergo RPLND almost always have their cancer recur and require subsequent chemotherapy. Thus, they appear to be at high risk for more widely disseminated disease and should be treated with chemotherapy instead of RPLND. This patient has no intermediate-risk or poor-risk features. Therefore, if repeat testing confirms a persistently increased or rising \( \beta \)-hCG level, standard treatment would be either 3 cycles of BEP or 4 cycles of EP. Two cycles of chemotherapy have not been tested in this population. Radiation therapy is not appropriate for this patient because radiation is not used in the treatment of NSGCTs. Surveillance is not appropriate in a patient with clear evidence of persistent disease.

4. (C) Start cycle 2 as originally scheduled at full dose. Chemotherapy for disseminated GCTs is potentially curative. Reasonable evidence indicates that outcomes may be compromised if either the dose is altered or the interval between treatments is increased. Therefore, the major protocols for first-line treatment have not delayed treatment or decreased doses in patients with reduced cell counts unless neutropenia was accompanied by fever.

5. (D) RPLND and chemotherapy. Cisplatin-based chemotherapy results in reduced sperm counts as well as abnormalities of sperm morphology and motility. These abnormalities often diminish or resolve with time, and many patients treated with cisplatin are subsequently able to father children. RPLND can result in anejaculation or retrograde ejaculation, which can make procreation impossible or at least unlikely. Although most men treated for testicular cancer appear to either retain or regain their fertility, a significant number do not. All patients undergoing either of these treatments should be encouraged to bank sperm to maximize the likelihood that they will be able to procreate in the future.

REFERENCES


