Overview of the treatment of testicular germ cell tumors

Author: William K Oh, MD
Section Editor: Jerome P Richie, MD, FACS
Deputy Editor: Sonali Shah, MD

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INTRODUCTION

Testicular cancers are among the most curable solid neoplasms; the five-year survival rate is over 95 percent. Initial therapy of early stage testicular germ cell tumors (GCTs) is based on histology and tumor extent.

An overview of therapy for males with testicular GCTs is presented here. The clinical manifestations, diagnosis, and staging are presented separately, as are more detailed discussions of specific clinical scenarios.

- (See "Clinical manifestations, diagnosis, and staging of testicular germ cell tumors".)
- (See "Treatment of stage I seminoma".)
- (See "Treatment of stage II seminoma".)
- (See "Management of stage I nonseminomatous germ cell tumors".)
- (See "Management of stage II nonseminomatous germ cell tumors".)
- (See "Initial risk-stratified treatment for advanced testicular germ cell tumors", section on 'Definition of risk'.)

INITIAL DIAGNOSIS AND MANAGEMENT

The diagnosis of a testicular malignancy is generally established at radical orchiectomy, which also serves as the initial treatment for the primary tumor. Subsequent therapy depends on the presence or absence of more extensive disease, histology, or other risk factors (algorithm 1 and algorithm 2 and algorithm 3).

Whenever possible, a baseline sperm count and sperm banking should be performed prior to orchiectomy and further therapy. Semen cryopreservation should be made available to all males diagnosed with testicular cancer prior to instituting therapy if they wish to preserve fertility. (See "Clinical manifestations, diagnosis, and staging of testicular germ cell tumors", section on 'Cryopreservation of sperm'.)

For males who present with clinically advanced disease, we perform a radical orchiectomy prior to chemotherapy whenever possible. Despite this, there are some males who present with life-threatening advanced disease who undergo systemic chemotherapy prior to orchiectomy ("delayed orchiectomy"). In such patients, the diagnosis should be obtained by biopsy of a metastatic lesion prior to treatment. (See "Radical inguinal orchiectomy for testicular germ cell tumors".)

SEMINOMA VERSUS NONSEMINOMATOUS GERM CELL TUMORS

The final pathology analysis is used to stratify testicular germ cell tumors (GCTs) into seminomas and nonseminomatous germ cell tumors (NSGCTs). These differ in clinical and biologic behavior.

- Seminomas are more likely to present with localized disease. Approximately 80 percent of males with seminomas present with stage I disease (limited to the testicle), while 15 percent have stage II disease (limited to retroperitoneal nodes) (table 1 and table 2). Fewer than 5 percent of patients have spread beyond the retroperitoneal nodes at presentation.

- Seminomas display relatively indolent growth and a longer natural history, and they rarely spread via the bloodstream beyond the retroperitoneal lymph nodes to other areas (eg, liver, lung, bones, or brain). Stage III metastases occur more frequently in males with NSGCTs.

- Seminomas typically do not have marked elevation of serum beta-human chorionic gonadotropin (beta-hCG) and never have an elevated alpha-fetoprotein (AFP). Seminoma with an elevated serum AFP is considered a mixed GCT, and these cancers are treated as NSGCTs. In contrast, beta-hCG and AFP are elevated in the majority of males with NSGCTs. (See "Serum tumor markers in testicular germ cell tumors".)

- Seminomas are exquisitely sensitive to radiation therapy, while NSGCTs are more radioresistant

EARLY STAGE DISEASE

Stage I testicular germ cell tumors (GCTs) are limited to the testis, and stage II disease is limited to the testis and retroperitoneal lymph nodes, without evidence of more distant disease. For stages I and II, treatment differs based on histology.

For both seminoma and nonseminomatous germ cell tumors (NSGCTs), the initial treatment decisions are based on clinical staging following radical inguinal orchiectomy.

Seminoma

Stage I seminoma — For patients with stage I seminoma (table 1 and table 2), orchiectomy is usually curative. (See "Treatment of stage I seminoma".)

- For patients who are able to comply with follow-up, we suggest active surveillance rather than chemotherapy or adjuvant radiation therapy (RT). Given the excellent prognosis, active surveillance minimizes the risks of treatment-associated morbidity. (See "Treatment of stage I seminoma" and "Treatment of stage I seminoma", section on 'Active surveillance'.)

- For males who refuse active surveillance and for those who want more aggressive treatment despite their excellent prognosis, we suggest one or two cycles of single-agent carboplatin (dosed at an area under the concentration x time curve [AUC] of 7) rather than adjuvant RT. Single-agent carboplatin is well tolerated and as effective as adjuvant RT in preventing relapse. It is also associated with less morbidity, including lower risks of impaired fertility, second malignancy, or late cardiac disease. (See "Treatment of stage I seminoma", section on 'Men who decline active surveillance'.)

- For males who refuse active surveillance and are not candidates for chemotherapy, we suggest adjuvant RT. (See "Treatment of stage I seminoma", section on 'Men who decline active surveillance'.)

Stage II seminoma — Following orchiectomy, the optimal treatment for stage II disease depends on the extent of lymph node involvement (table 1 and table 2). (See "Treatment of stage II seminoma".)

- **Stage IIA** – For males with stage IIA disease (ie, diameter of involved nodes ≤2 cm), we suggest RT rather than chemotherapy. However, cisplatin-based combination chemotherapy is a reasonable alternative. (See "Treatment of stage II seminoma", section on 'Stage IIA disease'.)

- **Stage IIB or IIC** – For males with more extensive retroperitoneal adenopathy (ie, diameter of involved nodes >2 cm), we recommend cisplatin-based chemotherapy. (See "Treatment of stage II seminoma", section on 'Stage IIB and IIC seminoma'.)

- **Elevated beta-hCG** – Although uncommon, males with pure seminoma may have associated elevations in serum beta-human chorionic gonadotropin (beta-hCG; >50 international units/L). While its clinical significance is controversial, we suggest treatment using cisplatin-based chemotherapy. (See "Treatment of stage II seminoma".)

  The optimal chemotherapy regimen has not been definitively established. The author's preference is for three courses of bleomycin, etoposide, and cisplatin (BEP (table 3)), but four courses of etoposide and cisplatin (EP) is an alternative. A choice between them should be based on institutional practice and the predicted ability of the patient to tolerate bleomycin.

Nonseminomatous germ cell tumor — The staging of patients with NSGCT is based on tumor markers following radical orchiectomy, as well as on clinical staging. For those patients whose treatment includes retroperitoneal lymph node dissection (RPLND), pathologic staging may result in further changes in treatment.

Stage IA and IB nonseminomatous germ cell tumors — For males with stage IA and IB NSGCTs, management depends on whether factors associated with an increased risk of relapse are present. These include:

- Lymphovascular invasion
- Predominance of an embryonal carcinoma component
- A T3 or T4 primary tumor

Using these risk factors, our approach to stage I NSGCTs is as follows:

- **Low risk** – For males who do not have any risk factors present, we suggest active surveillance. (See "Active surveillance following orchiectomy for stage I testicular germ cell tumors", section on 'General principles'.)

- **High risk** – For males with one or more risk factors, active surveillance, chemotherapy, and RPLND are all options. If technical expertise is available, RPLND is an appropriate treatment option. However, chemotherapy (one or two cycles of BEP) is a reasonable alternative (table 3). For males who prefer not to undergo further treatment, active surveillance is a reasonable alternative. However, these males should understand that their risk of relapse, and thus the need for subsequent treatment at a later date,

approaches 40 percent. (See "Management of stage I nonseminomatous germ cell tumors".)

Stage IS — Patients with NSGCT limited to the testis on clinical staging but who have persistent elevation of tumor markers following orchiectomy are classified as stage IS. Persistently elevated markers generally indicate the presence of metastatic disease. These patients should be treated with chemotherapy similarly to those with good-risk stage III disease. (See "Initial risk-stratified treatment for advanced testicular germ cell tumors".)

Stage II nonseminomatous germ cell tumors — For patients with stage II NSGCTs, treatment depends on whether disease is documented clinically or pathologically. (See "Management of stage II nonseminomatous germ cell tumors".)

- **Clinical stage IIA NSGCT** – For males with radiographically abnormal nodal involvement ≤2 cm and normal serum tumor markers, we suggest RPLND. Further treatment will be based on the pathologic stage. (See "Retroperitoneal lymph node dissection for early-stage testicular germ cell tumors", section on 'RPLND-II'.)

- **Clinical stage IIB and IIC NSGCT** – For males with radiographically detected nodal disease ≥2 cm and/or elevated serum tumor markers following orchiectomy, we suggest primary cisplatin-based combination chemotherapy. BEP for three cycles and EP for four cycles are acceptable regimens (table 3). (See "Management of stage I nonseminomatous germ cell tumors".)

- **Pathologic stage II NSGCT** – Males with NSGCTs with confirmed pathological node involvement following RPLND have pathologic stage II NSGCTs (table 2). Treatment following RPLND is based on the extent of nodal involvement (see "Management of stage II nonseminomatous germ cell tumors", section on 'Pathologic stage IIA disease'):

  - For males with lymph node metastases ≤2 cm in greatest diameter and with fewer than four lymph nodes involved, we suggest surveillance. While adjuvant chemotherapy dramatically reduces the relapse rate, treatment has no significant effect on survival because patients who relapse are treated with chemotherapy for curative intent.

  - For males with nodal involvement >2 cm and/or more than four lymph nodes involved, we suggest two cycles of adjuvant cisplatin-based combination chemotherapy (BEP) because the relapse risk is relatively higher.

ADVANCED DISEASE

For males with advanced testicular germ cell tumors (GCTs), management does not differ for seminoma and nonseminomatous germ cell tumors (NSGCTs).

Instead, treatment is selected based on the International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratification system (table 4). Males with seminoma are categorized as having good- or intermediate-risk disease. Males with NSGCTs are categorized as having good-, intermediate-, or poor-risk disease based on the sites of disease involvement and tumor marker levels. (See "Initial risk-stratified treatment for advanced testicular germ cell tumors", section on 'Definition of risk'.)

Good-risk disease — For males with good-risk disease, we recommend cisplatin-based combination chemotherapy. Our standard treatment is three cycles of bleomycin, etoposide, and cisplatin (BEP (table 3)). We prefer BEP rather than etoposide and cisplatin (EP) for males with good-risk GCTs. We reserve four cycles of EP for males with compromised pulmonary function, males with compromised renal function, and those over the age of 50 years. (See "Initial risk-stratified treatment for advanced testicular germ cell tumors", section on 'Good risk'.)

Intermediate- or poor-risk disease — For males with intermediate-risk or poor-risk disease, we recommend four cycles of BEP (table 3). An alternative regimen consists of etoposide, ifosfamide, and cisplatin (VIP (table 5)), which is preferred for patients at risk of bleomycin-induced lung injury.

Although high-dose chemotherapy with autologous stem cell transplantation is a promising approach, we suggest not administering high-dose chemotherapy as first-line treatment for poor-risk GCTs outside of a clinical trial. (See "Initial risk-stratified treatment for advanced testicular germ cell tumors", section on 'Intermediate- and poor-risk advanced disease'.)

For all patients with advanced disease treated with chemotherapy, a computed tomography (CT) scan of the chest, abdomen, and pelvis is obtained after treatment completion; this is particularly important for males who had initial evidence of retroperitoneal adenopathy. The use of surveillance imaging to assess for recurrent disease is discussed separately. (See "Posttreatment follow-up for men with testicular germ cell tumors", section on 'Guidelines for follow-up'.)

MANAGEMENT AFTER PRIMARY TREATMENT

The management of males postorchiectomy depends on the histologic type of germ cell tumor (GCT) and whether or not residual disease is identified:

Seminoma

- We suggest posttreatment surveillance if there is no evidence of residual disease. In addition, we suggest posttreatment surveillance rather than surgical resection if there is any residual mass <3 cm in size. (See "Treatment of stage II seminoma", section on 'Posttherapy residual masses'.)

- We perform a fludeoxyglucose (FDG)-positron emission tomography (PET) scan if there is evidence of residual masses ≥3 cm to determine appropriate treatment.

  - If the PET scan is negative, we suggest posttreatment surveillance. (See "Treatment of stage II seminoma", section on 'Posttherapy residual masses'.)

  - A positive PET scan indicates the presence of residual disease. In this situation, we suggest resection. Following resection of residual masses that contain viable GCT, we suggest two additional courses of chemotherapy. (See "Approach to surgery following chemotherapy for advanced testicular germ cell tumors".)

  - If resection of residual disease is not technically feasible, we recommend surveillance. Second-line chemotherapy should be deferred until there is evidence of disease progression by imaging. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors".)

Nonseminomatous germ cell tumor

- For males who have normalized their serum tumor markers but have imaging evidence of ≥1 retroperitoneal lymph node(s) larger than 1 cm, we perform a retroperitoneal lymph node dissection (RPLND). If RPLND is not performed, we proceed with posttreatment surveillance. (See "Approach to surgery following chemotherapy for advanced testicular germ cell tumors".)

- There is no consensus on the best approach to manage males with persistently elevated serum tumor markers that are either stable or sluggishly declining at the end of treatment. Although they are at a high risk of relapse, we do not suggest administration of additional chemotherapy. We offer either postchemotherapy RPLND or surveillance. A choice depends on patient preference and whether the expertise to perform an RPLND is available. (See "Approach to surgery following chemotherapy for advanced testicular germ cell tumors", section on 'Retroperitoneal lymph node dissection'.)

POSTTREATMENT SURVEILLANCE

Guidelines for surveillance following treatment are a function of histology (seminoma versus nonseminomatous germ cell tumor [NSGCT]) and the stage of disease at presentation. These guidelines are discussed in detail separately. (See "Posttreatment follow-up for men with testicular germ cell tumors", section on 'Guidelines for follow-up'.)

Periodic surveillance of the serum concentrations of beta-human chorionic gonadotropin (beta-hCG) and alpha-fetoprotein (AFP) is the most sensitive means of detecting early relapse for males with NSGCTs.

For males with seminoma, the value of monitoring serum tumor markers is unclear, as relapse is almost always detected by examination or by imaging. (See "Serum tumor markers in testicular germ cell tumors" and "Posttreatment follow-up for men with testicular germ cell tumors".)

Most patients who relapse do so within the first one to two years after their initial treatment. Relapses after two years are uncommon, and relapses after five years are rare. The intensity of follow-up is dictated by the histology of the original tumor (seminoma versus NSGCT), and the stage and risk of recurrence at original presentation.

TREATMENT OF RELAPSED OR REFRACTORY GERM CELL TUMORS

The optimal treatment of relapsed germ cell tumors (GCTs) depends on the response to prior therapy, the location and timing of the relapse, and the tumor histology. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors".)

- Males who are chemotherapy naïve at the time of recurrence should be treated with a cisplatin-based combination regimen (bleomycin, etoposide, and cisplatin [BEP] or etoposide and cisplatin [EP] (table 3 and table 6)). Retroperitoneal lymph node dissection (RPLND) is an alternative to chemotherapy in properly selected patients. (See "Initial risk-stratified treatment for advanced testicular germ cell tumors".)

- For males who relapse following postorchiectomy chemotherapy, we recommend combination chemotherapy using etoposide, ifosfamide, and cisplatin (VIP (table 5)). Other options include vinblastine or paclitaxel with ifosfamide plus cisplatin (VeIP (table 7) or TIP (table 8)).

- For males who were not previously treated with etoposide, we suggest VIP (table 5) or TIP (table 8), as discussed separately. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors", section on 'Treatment after initial chemotherapy'.)

- Males who relapse during or within four weeks after initial chemotherapy have platinum-refractory disease. These males have a poor prognosis and should be treated with a high-dose chemotherapy regimen with autologous hematopoietic cell transplantation (HCT) or in a clinical trial. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors", section on 'Platinum-refractory disease'.)

- Late-relapsing tumors are uncommon and tend to grow slowly. Treatment consists of an aggressive surgical approach and systemic chemotherapy. Surgical resection appears to be crucial for long-term survival. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors", section on 'Late relapse'.)

- Brain metastases may present as an isolated manifestation of metastatic disease or in conjunction with other systematic metastases. Systemic chemotherapy is usually preferred for initial treatment. However, in selected cases, chemotherapy may be used in combination with brain radiation therapy and/or surgical resection. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors", section on 'Brain metastases'.)

SPECIAL CONSIDERATIONS DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has increased the complexity of cancer care. Important issues include balancing the risk from treatment delay versus harm from COVID-19, minimizing the use of immunosuppressive cancer treatments whenever possible, mitigating the negative impacts of social distancing during care delivery, and appropriately and fairly allocating limited healthcare resources. These and other recommendations for cancer care during active phases of the COVID-19 pandemic are discussed separately. (See "COVID-19: Considerations in patients with cancer".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Testicular cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading

level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Testicular cancer (The Basics)")
- Beyond the Basics topic (see "Patient education: Testicular cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Prognosis** – Testicular germ cell tumors (GCTs) are among the most curable solid neoplasms, with five-year survival rates of approximately 95 percent. (See 'Introduction' above.)
- **Diagnosis** – The diagnosis of a testicular malignancy is generally established at radical orchiectomy, which also serves as the initial treatment for the primary tumor. (See "Clinical manifestations, diagnosis, and staging of testicular germ cell tumors".)
- **Risk stratification** – Optimal therapy requires estimating the likelihood of recurrence so that therapy can be limited when appropriate. Key elements in risk stratification include the histology (seminoma versus nonseminomatous germ cell tumor [NSGCT]), the presence or absence of metastases, and the degree of elevation in serum tumor markers (table 4). (See 'Introduction' above.)
- **Semen cryopreservation** – Whenever possible, a baseline sperm count and sperm banking should be performed prior to diagnosis and staging. Semen cryopreservation should be made available to all males prior to instituting therapy if they wish to preserve fertility. (See "Clinical manifestations, diagnosis, and staging of testicular germ cell tumors", section on 'Cryopreservation of sperm'.)
- **Initial management of early stage seminoma** – The initial management of early stage seminoma is as follows (algorithm 1):

- **Stage I seminoma** – For patients with a stage I seminoma, an extremely high cure rate can be achieved with radical orchiectomy. This is typically followed by active surveillance, but radiation therapy (RT) to paraaortic lymph nodes or single-agent carboplatin chemotherapy may be indicated if active surveillance is not appropriate. (See 'Stage I seminoma' above and "Treatment of stage I seminoma".)

- **Stage II seminoma** – Males with stage II seminoma are usually managed with RT or cisplatin-based combination chemotherapy, depending on the extent of retroperitoneal disease. (See 'Stage II seminoma' above and "Treatment of stage II seminoma".)

- **Initial management of early stage NSGCT** – The initial management of early stage NSGCT is as follows (algorithm 3):

  - **Stage IA and IB NSGCTs** – For males with stage IA and IB NSGCTs, the management approach is based on the presence or absence of specific risk factors for recurrence: vascular or lymphatic invasion, embryonal carcinoma comprising >40 percent of the total tumor volume, the presence of yolk sac elements, or elevated serum tumor markers prior to orchiectomy that do not decrease by expected half-life. (See 'Stage IA and IB nonseminomatous germ cell tumors' above and "Management of stage I nonseminomatous germ cell tumors".)

    - For males who do not have any risk factors present, we suggest active surveillance. (See "Active surveillance following orchiectomy for stage I testicular germ cell tumors".)

    - For males with risk factors, we suggest a retroperitoneal lymph node dissection (RPLND). However, two cycles of a cisplatin-based regimen are a reasonable alternative to surgery and are frequently the treatment of choice in Europe. (See "Retroperitoneal lymph node dissection for early-stage testicular germ cell tumors".)

  - **Stage IS NSGCTs** – Males with persistently elevated tumor markers following orchiectomy but without other evidence of disease (stage IS) should be treated with chemotherapy similar to those with good-risk stage III disease. (See "Initial risk-stratified treatment for advanced testicular germ cell tumors", section on 'Good risk'.)

  - **Stage II NSGCTs** – For males with stage II NSGCTs, treatment depends on the extent of disease and whether retroperitoneal lymph node involvement is documented pathologically or is based on imaging studies. Treatment options include RPLND,

surveillance, or the use of cisplatin-based combination chemotherapy. (See 'Stage II nonseminomatous germ cell tumors' above.)

For males with pathologic stage II NSGCTs following RPLND, treatment is based on the extent of nodal involvement (see "Management of stage II nonseminomatous germ cell tumors", section on 'Pathologic stage IIA disease'):

- For males with lymph node metastases ≤2 cm in greatest diameter, we suggest surveillance (**Grade 2C**).
- For males with nodal involvement >2 cm, we suggest adjuvant combination chemotherapy (**Grade 2C**). Our approach is to use two cycles of cisplatin-based chemotherapy.

- **Advanced disease** – Males with advanced disease are classified into good-, intermediate-, and poor-risk groups using the International Germ Cell Cancer Collaborative Group (IGCCCG) risk stratification system (table 4). The IGCCCG system takes into account primary tumor site, metastatic disease, and serum tumor marker levels. (See 'Advanced disease' above and "Initial risk-stratified treatment for advanced testicular germ cell tumors".)
  - **Good-risk disease** – For males with good-risk disease, we recommend cisplatin-based combination chemotherapy (**Grade 1A**). Our standard treatment is three cycles of bleomycin, etoposide, and cisplatin (BEP (table 3)). However, males with compromised pulmonary function or those who are at risk for bleomycin-induced lung injury should be treated with etoposide and cisplatin (EP) (table 6).
  - **Intermediate-risk or poor-risk disease** - For males with intermediate-risk or poor-risk disease, we recommend four cycles of BEP. An alternative regimen consists of etoposide, ifosfamide, and cisplatin (VIP) and is preferred for patients at risk of bleomycin-induced lung injury (table 5).
- **Management after primary treatment** – Following adjuvant treatment, a posttreatment computed tomography (CT) scan should be obtained. This is particularly important for males who had initial evidence of retroperitoneal adenopathy. (See 'Management after primary treatment' above.)
  - **Seminoma** – For males with seminoma with evidence of residual disease <3 cm in size, we suggest posttreatment surveillance rather than surgical resection. We perform a

fludeoxyglucose (FDG)-positron emission tomography (PET) scan to better characterize residual masses ≥3 cm. (See 'Seminoma' above.)

- If the PET scan is negative, we suggest posttreatment surveillance.
- If the PET scan is positive, we suggest resection of residual disease. If resection is not technically feasible, we suggest surveillance rather than initiation of second-line chemotherapy. (See "Treatment of stage II seminoma", section on 'Posttherapy residual masses' and 'Treatment of relapsed or refractory germ cell tumors' above.)

- **NSGCTs** – For males with NSGCTs, residual masses are commonly seen on postchemotherapy imaging studies.
  - For males who have normalized their serum tumor markers following treatment but have imaging evidence of ≥1 retroperitoneal lymph node(s) larger than 1 cm in diameter, an RPLND should be performed. If RPLND is not performed, we proceed with posttreatment surveillance. (See "Approach to surgery following chemotherapy for advanced testicular germ cell tumors", section on 'Retroperitoneal lymph node dissection'.)
  - For males with persistently elevated serum tumor markers that are either stable or sluggishly declining at the end of treatment, we offer either postchemotherapy RPLND or surveillance. A choice depends on patient preference and whether the expertise to perform an RPLND is available. (See "Approach to surgery following chemotherapy for advanced testicular germ cell tumors", section on 'Retroperitoneal lymph node dissection'.)

- **Posttreatment surveillance** – Periodic surveillance of the serum concentrations of beta-human chorionic gonadotropin (beta-hCG) and alpha-fetoprotein (AFP) is the most sensitive means of detecting early relapse for males with NSGCTs. For males with seminoma, the value of monitoring serum tumor markers is unclear, as relapse is almost always detected by examination or by imaging. (See 'Posttreatment surveillance' above.)

- **Treatment of relapsed or refractory disease** – The optimal treatment of relapsed GCTs depends on the response to prior therapy, the location and timing of the relapse, and the tumor histology. (See 'Treatment of relapsed or refractory germ cell tumors' above.)
  - Males who are chemotherapy naïve at the time of recurrence should be treated with a cisplatin-based combination regimen (eg, BEP (table 3)). RPLND is an alternative to

chemotherapy in properly selected patients. (See "Initial risk-stratified treatment for advanced testicular germ cell tumors".)

- For males who relapse following postorchiectomy chemotherapy without previous exposure to etoposide, we administer either VIP (table 5) or paclitaxel, cisplatin, and ifosfamide (TIP (table 8)), as discussed separately. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors", section on 'Treatment after initial chemotherapy'.)

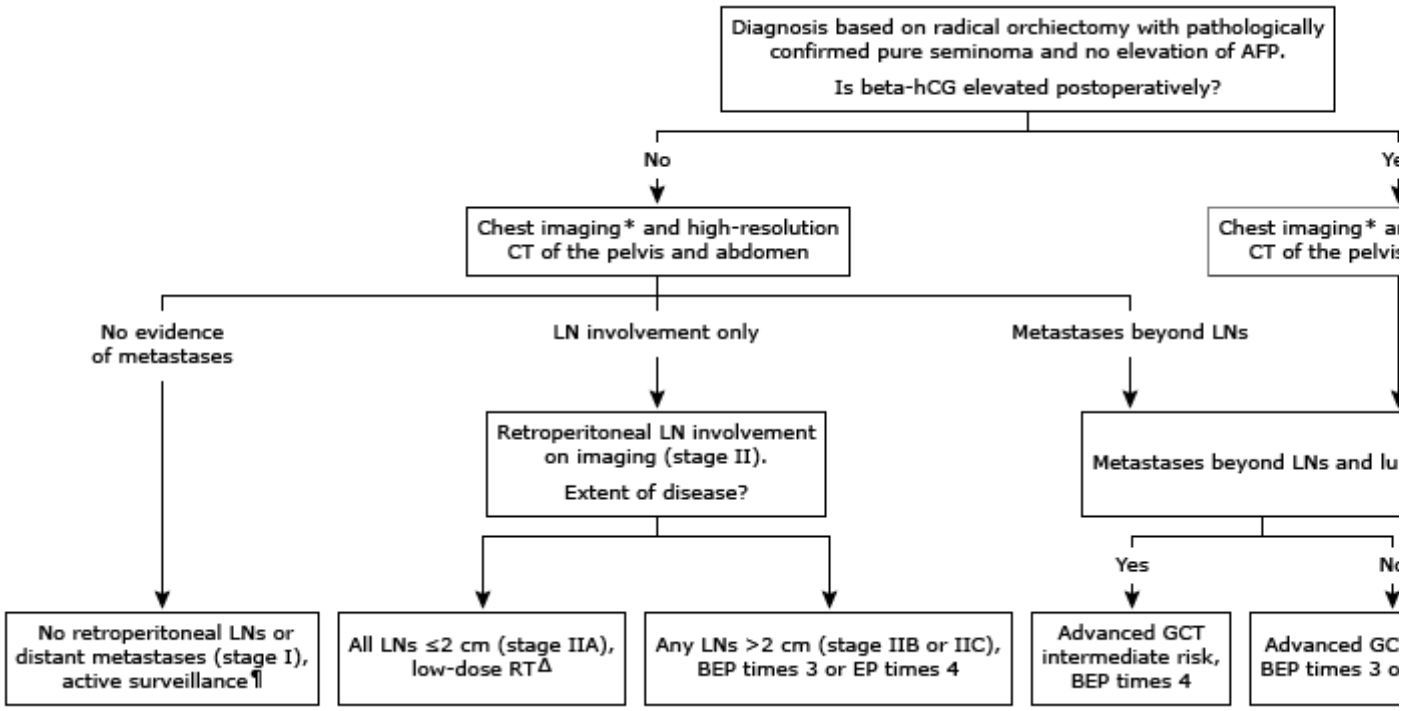
- Males who relapse during or within four weeks after initial chemotherapy have platinum-refractory disease. These males should undergo high-dose chemotherapy with autologous hematopoietic cell transplantation (HCT). (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors", section on 'Platinum-refractory disease'.)

- Relapses after two years are uncommon. An aggressive surgical approach in addition to systemic therapy should be adopted in these patients, since resection appears to be crucial to achieving long-term survival. (See "Diagnosis and treatment of relapsed and refractory testicular germ cell tumors", section on 'Late relapse'.)

Topic 2960 Version 51.0

GRAPHICS

Initial management of men with testicular seminoma



AFP: alpha-fetoprotein; beta-hCG; beta-human chorionic gonadotropin; CT: computed tomography; LN: lymp radiation therapy; BEP: bleomycin, etoposide, and cisplatin; EP: etoposide and cisplatin; GCT: germ cell tumo

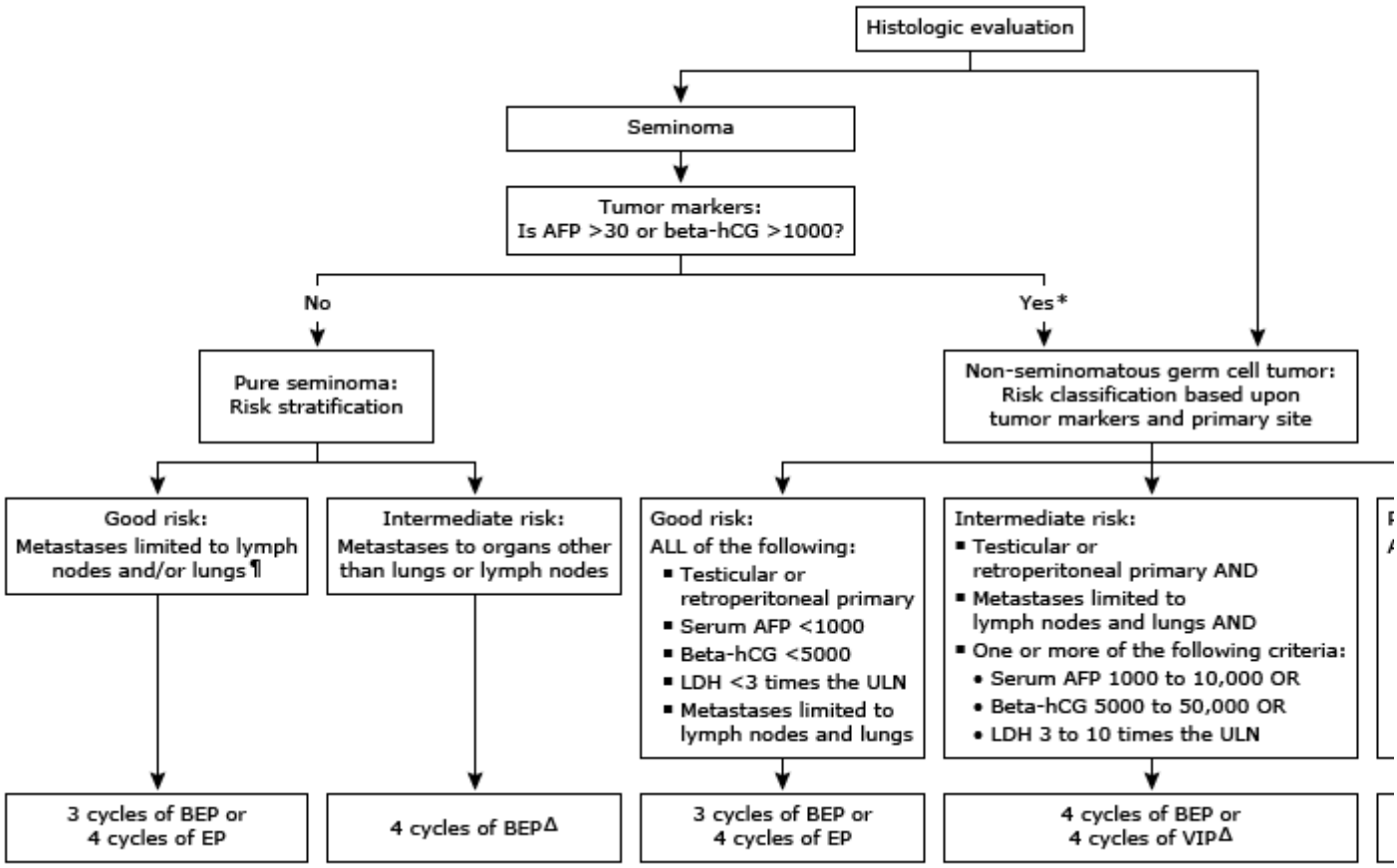
* Chest CT for all patients with positive LNs; chest radiograph for those with stage I seminoma.

¶ Adjuvant chemotherapy is an alternative for management for men who want to minimize the risk of recur those in whom surveillance is not an option and who refuse chemotherapy, adjuvant RT may be indicated.

Δ Combination cisplatin-based chemotherapy is an alternative for patients in whom RT is not feasible.

Graphic 112840 Version 1.0

Risk stratification and initial chemotherapy for men with metastatic germ cell



AFP: alpha-fetoprotein; beta-hCG: beta-human chorionic gonadotropin; LDH: lactate dehydrogenase; ULN: u normal; BEP: bleomycin, etoposide, cisplatin; EP: etoposide, cisplatin; VIP: ifosfamide, etoposide, cisplatin.

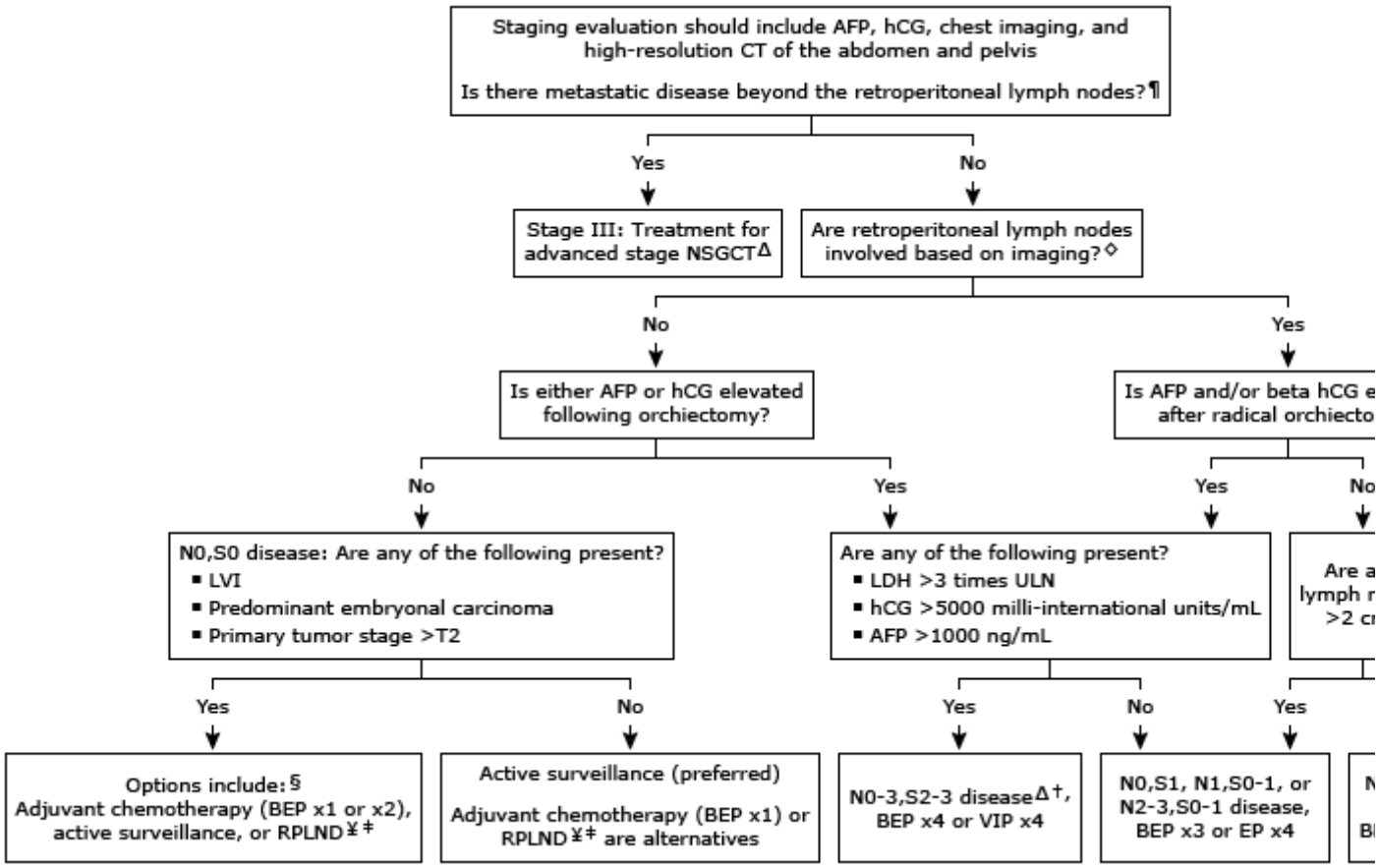
* Patients with elevated tumor markers are considered to have non-seminomatous germ cell tumors, even i consistent with seminoma.

¶ For patients with good-risk seminoma and LDH greater than 2.5 times ULN, we treat using an approach si intermediate-risk seminoma.

Δ For intermediate- and poor-risk disease, 4 cycles of BEP is generally preferred. 4 cycles of VIP is preferred i primary, mediastinal non-seminomatous germ cell tumor or any contraindication to bleomycin.

Graphic 112243 Version 2.0

Management of NSGCT following radical orchiectomy*



NSGCT: nonseminomatous germ cell tumor; AFP: alpha-fetoprotein; hCG: human chorionic gonadotropin; C computed tomography; LVI: lymphovascular invasion; LDH: lactate dehydrogenase; ULN: upper limit of norr bleomycin, etoposide, and cisplatin; RPLND: retroperitoneal lymph node dissection; VIP: etoposide, ifosfami cisplatin; EP: etoposide and cisplatin; MRI: magnetic resonance imaging.

* Patients with pure seminoma on pathology but with an elevated AFP are considered to have NSGCT.

¶ Inguinal or pelvic lymph nodes are classified as distant metastases and constitute stage III disease.

Δ Treatment for systemic disease is discussed in the topic on risk stratification and treatment of advanced di

◇ Involved lymph nodes are those with a short axis ≥10 mm.

§ All options are associated with a very high probability of cure. Choice is based upon a consideration of pati preference and available expertise.

¥ If RPLND is negative or reveals only teratoma, no further therapy is indicated. For men with tumors contai elements of embryonal carcinoma, seminoma, yolk sac tumor, and/or choriocarcinoma, options include eith adjuvant chemotherapy or careful surveillance. Refer to discussion in the topic on stage II NSGCT.

‡ RPLND should be limited to centers with adequate surgical expertise.

† Further evaluation should include MRI of the brain to rule out brain metastases.

Graphic 114315 Version 1.0

Testicular cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
Clinical T (cT)	
cT category	**cT criteria**
cTX	Primary tumor cannot be assessed
cT0	No evidence of primary tumor
cTis	Germ cell neoplasia *in situ*
cT4	Tumor invades scrotum with or without vascular/lymphatic invasion
NOTE: Except for Tis confirmed by biopsy and T4, the extent of the primary tumor is classified by radical orchiectomy. TX may be used for other categories for clinical staging.	
Pathological T (pT)	
pT category	**pT criteria**
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Germ cell neoplasia *in situ*
pT1	Tumor limited to testis (including rete testis invasion) without lymphovascular invasion
pT1a*	Tumor smaller than 3 cm in size
pT1b*	Tumor 3 cm or larger in size
pT2	Tumor limited to testis (including rete testis invasion) with lymphovascular invasion **or** Tumor invading hilar soft tissue or epididymis or penetrating visceral mesothelial layer covering the external surface of tunica albuginea with or without lymphovascular invasion
pT3	Tumor directly invades spermatic cord soft tissue with or without lymphovascular invasion
pT4	Tumor invades scrotum with or without lymphovascular invasion
* Subclassification of pT1 applies only to pure seminoma.	
Regional lymph nodes (N)	
Clinical N (cN)	
cN category	**cN criteria**
cNX	Regional lymph nodes cannot be assessed

cN0	No regional lymph node metastasis
cN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension **or** Multiple lymph nodes, none larger than 2 cm in greatest dimension
cN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension **or** Multiple lymph nodes, any one mass larger than 2 cm but not larger than 5 cm in greatest dimension
cN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Pathological N (pN)

pN category	**pN criteria**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or smaller in greatest dimension and less than or equal to five nodes positive, none larger than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass larger than 2 cm but not larger than 5 cm in greatest dimension; or more than five nodes positive, none larger than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass larger than 5 cm in greatest dimension

Distant metastasis (M)

M category	**M criteria**
M0	No distant metastases
M1	Distant metastases
M1a	Nonretroperitoneal nodal or pulmonary metastases
M1b	Nonpulmonary visceral metastases

Serum markers (S)¶

S category	**S criteria**
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH <1.5 × N$^{\Delta}$ **and** hCG (mIU/mL) <5000 **and** AFP (ng/mL) <1000
S2	LDH 1.5 to 10 × N$^{\Delta}$ **or** hCG (mIU/mL) 5000 to 50,000 **or** AFP (ng/mL) 1000 to 10,000
S3	LDH >10 × N$^{\Delta}$ **or** hCG (mIU/mL) >50,000 **or** AFP (ng/mL) >10,000

¶ Markers used for risk classification are postorchiectomy.
Δ N indicates the upper limit of normal for the LDH assay.

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; LDH: lactate dehydrogenase; hCG: human chorionic gonadotropin; AFP: alpha-fetoprotein.

Graphic 110731 Version 10.0

Testicular cancer TNM prognostic stage groups AJCC UICC 8th edition

When T is…	And N is…	And M is…	And S is…	Then the stage group is…
pTis	N0	M0	S0	0
pT1-T4	N0	M0	SX	I
pT1	N0	M0	S0	IA
pT2	N0	M0	S0	IB
pT3	N0	M0	S0	IB
pT4	N0	M0	S0	IB
Any pT/TX	N0	M0	S1-3	IS
Any pT/TX	N1-3	M0	SX	II
Any pT/TX	N1	M0	S0	IIA
Any pT/TX	N1	M0	S1	IIA
Any pT/TX	N2	M0	S0	IIB
Any pT/TX	N2	M0	S1	IIB
Any pT/TX	N3	M0	S0	IIC
Any pT/TX	N3	M0	S1	IIC
Any pT/TX	Any N	M1	SX	III
Any pT/TX	Any N	M1a	S0	IIIA
Any pT/TX	Any N	M1a	S1	IIIA
Any pT/TX	N1-3	M0	S2	IIIB
Any pT/TX	Any N	M1a	S2	IIIB
Any pT/TX	N1-3	M0	S3	IIIC
Any pT/TX	Any N	M1a	S3	IIIC
Any pT/TX	Any N	M1b	Any S	IIIC

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Graphic 110732 Version 8.0

Bleomycin, etoposide, and cisplatin (BEP) chemotherapy for germ cell tumors[1]

Cycle length: 21 days.
Total cycles: 3 to 4.*

Drug	Dose and route	Administration	Given on days
Bleomycin¶	30 units$^{\Delta}$ IV per dose	Dilute in 50 mL normal saline (NS) and administer over 10 minutes.	Days 1, 8, and 15
Etoposide	100 mg/m^2 IV per day	Dilute in 500 mL NS (concentration less than 0.4 mg/mL) and administer over one hour.	Days 1 through 5
Cisplatin	20 mg/m^2 IV per day	Dilute in 250 mL NS and administer over two hours. Do not administer with aluminum needles or intravenous sets.	Days 1 through 5

Pretreatment considerations:

Hydration	▪ Induction of diuresis using at least 2000 mL of NS minimizes the risk of cisplatin nephrotoxicity. Fluid administration should be adequate to establish a urine flow of at least 100 mL/hour for two hours prior to and two hours after cisplatin administration. ▪ Refer to UpToDate topic on "Cisplatin nephrotoxicity."
Emesis risk	▪ HIGH (>90% frequency of emesis). ▪ Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults."
Vesicant/irritant properties	▪ Bleomycin, etoposide, and cisplatin are classified as irritants. Cisplatin can cause significant tissue damage; avoid extravasation.[2] ▪ Refer to UpToDate topic on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants."
Infection prophylaxis	▪ Primary prophylaxis with granulocyte colony stimulating factors (G-CSF) is not indicated. ▪ Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation."
Dose adjustment for baseline liver or	▪ Bleomycin should not be administered in patients with a baseline creatinine >2.0 mg/dL. A lower initial dose of cisplatin or etoposide may be needed for patients with renal or hepatic dysfunction.[2,3]

renal dysfunction	▪ Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents" and "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Molecularly targeted agents" and "Chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency: Conventional cytotoxic agents."

Monitoring parameters:

- CBC with differential and platelet count weekly during treatment.
- Basic metabolic panel (creatinine and electrolytes) prior to each treatment cycle.
- Liver function tests prior to each treatment cycle.
- Assessment of baseline pulmonary function tests (PFTs), including a diffusing capacity for carbon monoxide (DLCO), should be performed prior to bleomycin treatment and repeated at intervals during therapy.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ Each cycle should begin on schedule regardless of the degree of myelosuppression.[1] If febrile neutropenia or thrombocytopenic bleeding occurs, a dose reduction of 25% for etoposide should be used for subsequent cycles. If neutrophil count remains ≤2500 cells/microL or platelets remain ≤100,000/microL, G-CSF should be administered. ▪ Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation."
Pulmonary toxicity	▪ Bleomycin can be associated with the development of life-threatening pulmonary toxicity. Maximum lifetime bleomycin dose should not exceed 400 mg. Discontinue bleomycin in patients with clinical or radiographic evidence of pulmonary injury, or decline in the DLCO of 25% or more, even if asymptomatic. Do not reintroduce bleomycin to patients with any bleomycin-induced lung injury.
Neurologic toxicity	▪ Neuropathy usually is seen after cumulative doses of cisplatin beyond 400 mg/m^2, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. Peripheral neuropathies can occur with prolonged courses (four to seven months) of cisplatin. Cisplatin treatment should be discontinued with the first signs and symptoms of the development of neurotoxicity.[2,5] ▪ Refer to UpToDate topic on "Overview of neurologic complications of platinum-based chemotherapy."

Renal toxicity	▪ Treatment in the setting of renal impairment (ie, creatinine >2.0 mg/dL or GFR <50 mL/min) requires a balanced discussion of the goals of treatment and the risks of cisplatin nephrotoxiciy in the face of impaired renal function.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; CBC: complete blood count; GFR: glomerular filtration rate.

* The precise number of cycles depends on the stage of the germ cell tumor.

¶ Cumulative lifetime dose of bleomycin should be limited to 400 units because of the increased rates of pulmonary toxicity. Refer to UpToDate topic on "Bleomycin-induced lung injury."

Δ 1 unit = 1 mg.

References:

1. *Nichols CR, et al. J Clin Oncol 1998; 16:1287.*
2. *Cisplatin injection, powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 8, 2011).*
3. *Etoposide injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 9, 2011).*
4. *Bleomycin sulfate injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 8, 2011).*
5. *Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2011; 29:4189.*

Graphic 65516 Version 39.0

Risk stratification system for advanced testicular germ cell tumors

Seminomas
Good risk
All of the following:
Any primary site
No metastases to organs other than the lungs and/or lymph nodes
Normal serum AFP
Intermediate risk
All of the following:
Any primary site
Metastases to organs other than the lungs and/or lymph nodes
Normal serum AFP
Nonseminomatous germ cell tumors
Good risk
All of the following:
Testicular or retroperitoneal primary tumors
No metastases to organs other than the lungs and/or lymph nodes
Serum AFP <1000 ng/mL, beta-hCG <5000 milli-international units/mL, and LDH <3 times the upper limit of normal*
Intermediate risk
All of the following:
Testicular or retroperitoneal primary tumors
No metastases to organs other than the lungs and/or lymph nodes
Serum AFP 1000 to 10,000 ng/mL* **or**
Serum beta-hCG 5000 to 50,000 milli-international units/mL* **or**
LDH 3 to 10 times the upper limit of normal*
Poor risk
Any of the following:
Mediastinal primary with or without metastases
Metastases to organs other than the lungs and/or lymph nodes
Serum AFP >10,000 ng/mL*

Serum beta-hCG >50,000 milli-international units/mL*
LDH more than 10 times the upper limit of normal*

AFP: alpha-fetoprotein; beta-hCG: beta-human chorionic gonadotropin; LDH: lactic dehydrogenase.

* Markers used for staging and risk classification are postorchiectomy.

Based on the guidelines of the International Germ Cell Cancer collaborative group.

Graphic 61906 Version 12.0

Cisplatin, etoposide, and ifosfamide for relapsed germ cell tumors (VIP)[1]

Cycle length: 21 days.
Total cycles: 4.

Drug	Dose and route	Administration	Given on days
Cisplatin	20 mg/m^2 IV per day	Dilute with 250 mL NS* and administer over one hour. Do not administer with aluminum needles or IV sets.	Days 1 to 5
Etoposide¶	75 mg/m^2 IV per day	Dilute with 500 mL NS* (concentration <0.4 mg/mL) and administer over one hour.	Days 1 to 5
Ifosfamide¶	1200 mg/m^2 per day IV infusion over a minimum of 30 minutes	Dilute with NS, D5W, or sterile water for injection* to a final concentration of 50 mg/mL.	Days 1 to 5
Mesna	120 mg/m^2 IV	Dilute with NS* and administer via slow IV push prior to day 1 infusion of ifosfamide. Total concentration of mesna should not exceed 20 mg/mL.	Day 1
Mesna$^\Delta$	1200 mg/m^2 per day continuous IV infusion	Dilute with NS* and administer as continuous infusion over 24 hours.[2] Total concentration of mesna should not exceed 20 mg/mL. Can mix with ifosfamide.	Days 1 to 5

Pretreatment considerations:

Hydration	▪ Induction of diuresis using IV NS minimizes the risk of cisplatin nephrotoxicity and ifosfamide bladder toxicity. At least 2000 mL of NS should be administered at a rate of 100 to 125 mL per hour throughout the five days of treatment and continued for at least two hours after the last doses of cisplatin/ifosfamide. ▪ Refer to UpToDate topics on "Cisplatin nephrotoxicity" and "Hemorrhagic cystitis in cancer patients".
Emesis risk	▪ HIGH (>90% frequency of emesis). ▪ Concomitant administration of aprepitant may increase the risk of ifosfamide neurotoxicity; it is avoided at many institutions. ▪ Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults".

Vesicant/irritant properties	▪ Cisplatin is an irritant but can cause significant tissue damage; avoid extravasation.[3] ▪ Refer to UpToDate topic on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants".
Infection prophylaxis	▪ Primary prophylaxis with G-CSF is administered as a routine component of this regimen.[1] ▪ Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation".
Dose adjustment for baseline liver or renal dysfunction	▪ Dose adjustment in the setting of baseline renal impairment (ie, creatinine >3.0 mg/dL or GFR <50 mL/min) requires a balanced discussion of the goals of treatment and the risks of cisplatin. ▪ A lower starting dose of ifosfamide may be needed in patients with pre-existing renal or liver impairment. ▪ Before starting treatment with ifosfamide, it is necessary to exclude or correct any urinary tract obstructions. ▪ Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents" and "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Molecularly targeted agents" and "Chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency: Conventional cytotoxic agents and "Hemorrhagic cystitis in cancer patients".

Monitoring parameters:

▪ CBC with differential and platelet count weekly during treatment.
▪ Assess liver function tests prior to each treatment cycle.
▪ Cisplatin is associated with significant nephrotoxicity. Ifosfamide is associated with cumulative nephrotoxicity, mostly at a total dose above 60 grams/m^2.[4] Clinical manifestations may include hypophosphatemia, renal potassium wasting, metabolic acidosis with a normal ion gap, and, rarely, polyuria due to nephrogenic diabetes insipidus. Assess creatinine and electrolytes, including potassium and phosphate, daily during treatment, and prior to each new treatment cycle. ▪ Refer to UpToDate topics on "Ifosfamide nephrotoxicity" and "Cisplatin nephrotoxicity".
▪ Mesna does not prevent hemorrhagic cystitis in all patients.[2] Perform urinalysis on a morning specimen of urine daily, on days 1 through 5. Refer to UpToDate topic on "Hemorrhagic cystitis in cancer patients".
▪ Monitor for ifosfamide-related neurotoxicity (confusion, coma, rarely seizures, weakness, neuropathy, ataxia, cranial nerve dysfunction) daily, on days 1 through 5. CNS side effects may be especially problematic for those over age 60.

▪ Refer to UpToDate topic on "Overview of neurologic complications of conventional non-platinum cancer chemotherapy".	
▪ Monitor vital signs during etoposide infusion.	
▪ Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ Unless clinically essential, a repeat course of therapy should not be started with a WBC count below 2000/μL and/or a platelet count below 50,000/μL. [4] ▪ Reduce doses of etoposide and ifosfamide each by 25% for subsequent cycles for granulocytopenic fever or thrombocytopenic bleeding with the previous course of therapy.[1]
Neurotoxicity	▪ Neuropathy usually is seen after cumulative doses of cisplatin beyond 400 mg/m^2, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. [3] ▪ Discontinue ifosfamide treatment for encephalopathy. ▪ Refer to UpToDate topics on "Overview of neurologic complications of conventional non-platinum cancer chemotherapy" and "Overview of neurologic complications of platinum-based chemotherapy".
Nephrotoxicity and urotoxicity	▪ It is recommended that subsequent doses of cisplatin be withheld until the serum creatinine is <3.0 mg/dL. ▪ If microscopic hematuria (greater than 10 RBCs per high-power field) is present during therapy, then subsequent administration of ifosfamide should be withheld until complete resolution. ▪ Refer to UpToDate topics on "Cisplatin nephrotoxicity" and "Hemorrhagic cystitis in cancer patients".
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; G-CSF: granulocyte-colony stimulating factors; GFR: glomerular filtration rate; CBC: complete blood count; CNS: central nervous system; WBC: white blood cell; RBC: red blood cell.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ The initial protocol included empiric reduction of etoposide and ifosfamide doses by 25% for patients who have received prior radiation therapy.[1]

Δ Due to a longer half-life of ifosfamide and associated metabolites at higher doses, some references recommend continuation of mesna for 12 to 24 hours beyond completion of ifosfamide to reduce the risk of hemorrhagic cystitis.[2]

References:

1. *Nichols CR, et al. J Clin Oncol 1998; 16:1287.*
2. *MESNA injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed September 19, 2019).*
3. *Cisplatin injection, powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on September 19, 2019).*
4. *Ifosfamide injection, powder, for solution . United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on September 19, 2019).*

Graphic 51451 Version 20.0

Cisplatin and etoposide for relapsed germ cell tumors[1]

Cycle length: 21 days.

Drug	Dose and route	Administration	Given on days
Cisplatin	20 mg/m^2 IV per day	Dilute with 250 mL normal saline (NS) and administer over one hour. Do not administer with aluminum needles or intravenous sets.	Days 1 through 5
Etoposide	100 mg/m^2 IV per day	Dilute with 500 mL NS (concentration less than 0.4 mg/mL) and administer over one hour.	Days 1 through 5

Pretreatment considerations:

Hydration	▪ Induction of diuresis using intravenous NS minimizes the risk of cisplatin nephrotoxicity. At least 2000 mL of NS should be administered at a rate of 100 to 125 mL per hour throughout the five days of treatment and continued for at least two hours after the last dose of cisplatin. ▪ Refer to UpToDate topic on "Cisplatin nephrotoxicity".
Emesis risk	▪ HIGH (>90% frequency of emesis). ▪ Aprepitant can be given orally (125 mg on day 1, 80 mg on days 2 and 3) with ondansetron, prochlorperazine, and dexamethasone daily. ▪ Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults".
Vesicant/irritant properties	▪ Both cisplatin and etoposide are irritants. Cisplatin can cause significant tissue damage; avoid extravasation.[2] ▪ Refer to UpToDate topic on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants".
Infection prophylaxis	▪ Primary prophylaxis with granulocyte colony stimulating factors is not indicated. ▪ Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation".
Dose adjustment for baseline liver or renal dysfunction	▪ Treatment in the setting of baseline renal dysfunction (creatinine >3.0 mg/dL or GFR <50 mL/min) requires a balanced discussion of the goals of treatment and the risks of administering cisplatin.[3] ▪ Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents" and "Chemotherapy hepatotoxicity and dose modification in patients with

	liver disease: Molecularly targeted agents" and "Chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency: Conventional cytotoxic agents".
Monitoring parameters:	
▪ CBC with differential weekly during treatment.	
▪ Basic metabolic panel (creatinine and electrolytes) prior to each treatment cycle.	
▪ Liver function tests prior to each treatment cycle.	
▪ Monitor vital signs during etoposide infusion.	
▪ Monitor for neurotoxicity; monitor for hearing loss prior to each dose of cisplatin; audiometry as clinical indicated.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ Each cycle should begin on schedule regardless of the degree of myelosuppression.[1] If febrile neutropenia or thrombocytopenic bleeding occurs, a dose reduction of 25% for etoposide should be used for subsequent cycles.
Neurologic toxicity	▪ Neuropathy usually is seen after cumulative doses of cisplatin beyond 400 mg/m^2, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. ▪ Refer to UpToDate topic on "Overview of neurologic complications of platinum-based chemotherapy".
Renal toxicity	▪ It is recommended that subsequent doses of cisplatin be withheld until the serum creatinine is less than 3.0 mg/dL.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; GFR: glomerular filtration rate; CBC: complete blood count.

References:

1. *Loehrer PJ, et al. J Clin Oncol 1995; 13:470.*
2. *Cisplatin injection, powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on December 20, 2011).*

3. *Etoposide injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed December 20, 2011).*

Graphic 63222 Version 17.0

Chemotherapy regimens for recurrent germ cell tumors: Vinblastine, ifosfamide, and cisplatin (VeIP)[1-3]

Cycle length: 21 days.
Total cycles: 4 cycles.

Drug	Dose and route	Administration	Given on days
Vinblastine	0.11 mg/kg per day* IV	Mix in 50 to 100 mL NS¶ and administer over 5 to 10 minutes.Δ	Daily, days 1 and 2
Cisplatin	20 mg/m^2 per day IV	Dilute in 250 mL NS¶ and administer over 30 to 60 minutes (or at 1 mg/min)◇ after vinblastine. Do not administer with aluminum needles or sets.	Daily, days 1 through 5
Mesna§	240 mg/m^2 IV bolus prior to each dose of ifosfamide, then 240 mg/m^2 IV bolus at 4 and 8 hours after the start of ifosfamide administration each day (total daily mesna dose of 720 mg/m^2).¥	Mix in 100 mL NS or D5W¶ and administer over 15 minutes. Total concentration of mesna should not exceed 20 mg/mL.[4]	Daily, days 1 through 5
Ifosfamide	1200 mg/m^2 per day* IV	Mix with NS or D5W¶ or sterile water for injection to a final concentration of 0.6 to 20 mg/mL and infuse over 3 hours.	Daily, days 1 through 5

Pretreatment considerations:

Hydration	▪ **Cisplatin:** Induction of diuresis minimizes the risk of cisplatin nephrotoxicity. Hydration with 1 to 2 L of IV fluids is recommended to establish adequate urinary output (>100 mL/hour) for at least 2 hours prior to and 2 hours after cisplatin administration. ▪ Alternatively, pretreatment hydration with 1 to 2 L of fluid infused for 8 to 12 hours prior to each dose of cisplatin.[5] ▪ Refer to UpToDate topic on "Cisplatin nephrotoxicity", section on "Prevention of nephrotoxicity".

	▪ **Ifosfamide:** Adequate hydration (at least 2 L of oral or IV fluids per day) should be maintained with ifosfamide to reduce the risk of ifosfamide bladder toxicity.[6] ▪ Refer to UpToDate topic on "Chemotherapy and radiation-related hemorrhagic cystitis in cancer patients".
Emesis risk	▪ **HIGH** (>90% frequency of emesis). ▪ Concomitant administration of a neurokinin 1 receptor antagonist (eg, aprepitant) may increase the risk of ifosfamide neurotoxicity; it is avoided at many institutions. ▪ Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting".
Prophylaxis for infusion reactions	▪ Routine prophylaxis not indicated for cisplatin, ifosfamide, or vinblastine. ▪ Refer to UpToDate topic on "Infusion reactions to systemic chemotherapy".
Vesicant/irritant properties	▪ Vinblastine is a vesicant and can cause significant tissue damage; avoid extravasation. ▪ Cisplatin is an irritant but can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topic on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants".
Infection prophylaxis	▪ Primary prophylaxis with hematopoietic growth factors is indicated since the incidence of neutropenic fever with this regimen was 39 and 71%, respectively, in two different studies.[1,2] ▪ Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation".
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose of vinblastine may be needed in patients with hepatic impairment. ▪ A lower starting dose of ifosfamide may be needed for patients with renal or liver impairment. ▪ The optimal approach to cisplatin therapy in patients with pre-existing renal impairment is unknown. Patients are typically treated with cisplatin regardless of renal function since treatment intent is curative, but appropriate clinical judgement is necessary. ▪ Before starting treatment, it is essential to exclude or correct any urinary tract obstruction. ▪ Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents" and "Chemotherapy nephrotoxicity and dose modification in patients with kidney impairment: Conventional cytotoxic agents".

Hemorrhagic cystitis prevention	▪ Mesna does not prevent hemorrhagic cystitis in all patients. ▪ Perform urinalysis on a morning specimen of urine for hematuria daily during ifosfamide administration. If microscopic hematuria (ie, greater than 10 RBCs per high-power field) is present, then subsequent administration of ifosfamide should be withheld until complete resolution.[6] ▪ Refer to UpToDate topic on "Chemotherapy and radiation-related hemorrhagic cystitis in cancer patients".
Neurotoxicity issues	▪ There is an increased risk of encephalopathy for those with prior history of ifosfamide-related encephalopathy, renal dysfunction, low serum albumin, and those with concomitant use of aprepitant or prior cisplatin treatment. Monitor for CNS toxicity and discontinue ifosfamide treatment for encephalopathy. ▪ Refer to UpToDate topic on "Overview of neurologic complications of conventional non-platinum cancer chemotherapy".
Ototoxicity	▪ Incidence of ototoxicity maybe increased when vinblastine is administered with ototoxic agents, including platinum agents.[7] Use caution in patients with prior hearing loss. ▪ Refer to UpToDate topic on "Overview of neurologic complications of platinum-based chemotherapy".

Monitoring parameters:

- CBC with differential and platelet count prior to each new treatment cycle.
- Assess electrolytes (especially potassium, magnesium, and phosphate) and renal function daily during administration and prior to each new treatment cycle.
- Assess liver function tests daily during administration and prior to each new treatment cycle.
- Check urinalysis (or urine dipstick) prior to and during ifosfamide administration to monitor for hemorrhagic cystitis.
- Monitor for ifosfamide-related neurotoxicity (eg, encephalopathy, coma, rarely seizures, weakness, neuropathy, ataxia, cranial nerve dysfunction) daily. Assess changes in neurologic function, including neuropathy and/or paresthesias, prior to each new treatment cycle.
- Refer to UpToDate topic on "Overview of neurologic complications of non-platinum cancer chemotherapy".
- Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.
- Monitor for constipation and/or ileus.

Suggested dose modifications for toxicity:

Myelosuppression	▪ For febrile neutropenia, thrombocytopenic bleeding event, or thrombocytopenia requiring transfusion, reduce vinblastine and

	ifosfamide doses by 25% each for subsequent courses.[1,2] ■ Patients with persistent myelosuppression on day 22 may still proceed with the next treatment cycle. Perform daily CBC. Omit the ifosfamide dose on day 5 if the WBC does not rise to >2.5 × 10^3 cells/mm^3 and platelets do not rise to >100 × 10^6 cells/mm^3.[1,2]
Hemorrhagic cystitis	■ Withhold further ifosfamide doses and continue the daily mesna dose if urinalysis shows 10 or more erythrocytes per high-powered field until hematuria is resolved.[1,2,6] ■ Refer to UpToDate topic on "Chemotherapy and radiation-related hemorrhagic cystitis in cancer patients".
Nephrotoxicity	■ **Cisplatin:** No dose adjustments for cisplatin were provided for this regimen, but the rates of grade 2, 3, and 4 nephrotoxicity were 25, 9, and 6%, respectively.[1] Among those with severe (grade 3 or 4) nephrotoxicity, the rates of irreversible nephrotoxicity were approximately 2% each.[1,2] ■ The United States Prescribing Information for cisplatin recommends that the drug be withheld until serum creatinine is <1.5 mg/dL and/or BUN is <25 mg/dL.[5] ■ For grade ≥2 nephrotoxicity during treatment (ie, creatinine >1.5 times normal value despite adequate hydration), reduce the dose of cisplatin if CrCl determined prior to the next cycle is <60 mL/min. ■ **Ifosfamide:** Reduce the ifosfamide dose by 25% for a serum creatinine ≥2 mg/dL.[1,2] ■ Ifosfamide is associated with cumulative nephrotoxicity and electrolyte abnormalities, mostly at a total dose above 60 g/m^2. Clinical manifestations may include hypophosphatemia, renal potassium wasting, metabolic acidosis with a normal ion gap, and, rarely, polyuria due to nephrogenic diabetes insipidus. ■ Refer to UpToDate topic on "Ifosfamide nephrotoxicity".
Neurologic toxicity	■ **Cisplatin:** Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m^2, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. ■ Refer to UpToDate topic on "Neurologic complications of platinum-based chemotherapy". ■ **Ifosfamide:** CNS toxicities can be severe and result in encephalopathy and death. CNS side effects may be especially problematic for those over age 60. Discontinue ifosfamide treatment for encephalopathy. ■ Refer to UpToDate topic on "Overview of neurologic complications of non-platinum cancer chemotherapy".

	▪ **Vinblastine:** Care must be taken to avoid constipation in patients receiving vincristine. For severe paresthesias and/or constipation, the dose of vinblastine should be reduced by 50%.[1] Vinblastine should be discontinued permanently if an adynamic ileus occurs. ▪ Refer to UpToDate topic on "Overview of neurologic complications of non-platinum cancer chemotherapy".
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

NS: normal saline; IV: intravenous; D5W: 5% dextrose in water; RBC: red blood cell; CNS: central nervous system; CBC: complete blood count; WBC: white blood cell; BUN: blood urea nitrogen; CrCl: creatinine clearance.

* In the original protocol, ifosfamide and vinblastine doses were reduced by 25% in patients with previous abdominal or chest radiotherapy.[1]

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Vinblastine should not be diluted in large volumes of diluent (ie, >100 mL) or given IV for prolonged periods (ie, >30 minutes), since this may result in vein irritation and risk of extravasation.

◇ Alternatively, may dilute in 2 L dextrose 5% and sodium chloride 0.45% or dextrose 5% and sodium chloride 0.3% containing 37.5 g of mannitol, and infuse over a 6- to 8-hour period.[5]

§ Due to a longer half-life of ifosfamide and associated metabolites, some references recommend continuation of mesna for 12 to 24 hours beyond completion of ifosfamide to reduce the risk of hemorrhagic cystitis. If necessary, oral mesna may be used at a dose twice that of IV mesna.

¥ The original protocol used a daily mesna dose of 400 mg/m^2 IV bolus prior to ifosfamide, followed by 1200 mg/m^2 per day continuous IV infusion.[1,2] Alternative administration schedules also exist and may vary by institution, including the use of continuous infusion mesna.

References:

1. *Loehrer PJ Sr, et al. Ann Intern Med 1988; 109:504.*
2. *Loehrer PJ Sr, et al. J Clin Oncol 1998; 16:2500.*
3. *Morales ASR, et al. J Oncol Pharm Practice 2020; supplements 1 and 2.*
4. *MESNA injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed September 9, 2021).*
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6. *Ifosfamide injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed September 9, 2021).*
7. *Vinblastine injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on September 9, 2021).*

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Chemotherapy regimens for relapsed testicular germ cell tumors: Paclitaxel, ifosfamide, and cisplatin (TIP)[1]

Cycle length: 21 days.
Total cycles: 4 cycles.

Drug	Dose and route	Administration	Given on days
Paclitaxel	250 mg/m^2 IV	Dilute in 1000 mL NS or D5W* and administer over 24 hours;¶ special tubing needed.	Day 1
Mesna$^{\Delta}$	300 mg/m^2 IV bolus prior to each dose of ifosfamide, then 300 mg/m^2 IV bolus at 4 and 8 hours after the start of ifosfamide administration each day (total daily mesna dose 900 mg/m^2)$^{\diamond}$	Mix in 100 mL NS or D5W* and administer over 15 minutes. Total concentration of mesna should not exceed 20 mg/mL.[2]	Daily, days 2 through 5
Ifosfamide	1500 mg/m^2 per day IV	Mix in 250 mL NS or D5W* or sterile water for injection to a final concentration of 0.6 to 20 mg/mL and infuse over 60 minutes.	Daily, days 2 through 5
Cisplatin	25 mg/m^2 per day IV	Dilute in 250 mL NS* and administer over 30 to 60 minutes (or at 1 mg/min).§ Do not administer with aluminum needles or sets.	Daily, days 2 through 5

Pretreatment considerations:

Hydration	▪ **Cisplatin:** Induction of diuresis minimizes the risk of cisplatin nephrotoxicity. Hydration with 1 to 2 L of IV fluids is recommended to establish adequate urinary output (>100 mL/hour) for at least 2 hours prior to and 2 hours after cisplatin administration.[3] ▪ Alternatively, pretreatment hydration with 1 to 2 L of fluid can be infused for 8 to 12 hours prior to each dose of cisplatin.[3] ▪ Refer to UpToDate topic on "Cisplatin nephrotoxicity", section on "Prevention of nephrotoxicity".

	▪ **Ifosfamide:** Adequate hydration (at least 2 L of oral or IV fluids per day) should be maintained with ifosfamide to reduce the risk of ifosfamide-related bladder toxicity.[4] ▪ Refer to UpToDate topics on "Chemotherapy and radiation-related hemorrhagic cystitis in cancer patients".
Emesis risk	▪ **HIGH** (>90% frequency of emesis). ▪ Concomitant administration of a neurokinin 1 receptor antagonist (eg, aprepitant) may increase the risk of ifosfamide neurotoxicity; it is avoided at many institutions. ▪ Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting".
Prophylaxis for infusion reactions	▪ Premedicate with dexamethasone plus both an H1 and an H2 receptor antagonist prior to paclitaxel administration.[5] Routine prophylaxis not indicated for cisplatin or ifosfamide. ▪ Refer to UpToDate topic on "Infusion reactions to systemic chemotherapy".
Vesicant/irritant properties	▪ Paclitaxel can cause significant tissue damage; avoid extravasation. ▪ Cisplatin is an irritant but can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topic on "Extravasation injury from chemotherapy and other non-antineoplastic vesicants".
Infection prophylaxis	▪ Primary prophylaxis with hematopoietic growth factors is indicated; despite the use of primary prophylaxis hematopoietic growth factors in this regimen, the incidence of neutropenic fever was 48%.[1] ▪ Refer to UpToDate topic on "Use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation".
Dose adjustment for baseline liver or renal dysfunction	▪ A lower starting dose of paclitaxel may be needed in patients with pre-existing liver impairment. ▪ A lower starting dose of ifosfamide may be needed for patients with pre-existing renal or liver impairment. ▪ The optimal approach to cisplatin therapy in patients with pre-existing renal impairment is unknown. Patients are typically treated with cisplatin regardless of renal function since treatment intent is curative, but appropriate clinical judgement is necessary. ▪ Before starting treatment, it is essential to exclude or correct any pre-existing urinary tract obstruction. ▪ Refer to UpToDate topics on "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents"

	and "Chemotherapy nephrotoxicity and dose modification in patients with kidney impairment: Conventional cytotoxic agents".
Hemorrhagic cystitis prevention	▪ Mesna does not prevent hemorrhagic cystitis in all patients. ▪ Perform urinalysis on a morning specimen of urine for hematuria daily during ifosfamide administration. If microscopic hematuria (ie, greater than 10 RBCs per high-power field) is present, then subsequent administration of ifosfamide should be withheld until complete resolution. ▪ Refer to UpToDate topic on "Chemotherapy and radiation-related hemorrhagic cystitis in cancer patients".
Neurotoxicity issues	▪ There is an increased risk of encephalopathy for those with prior history of ifosfamide-related encephalopathy, renal dysfunction, low serum albumin, and those with concomitant use of aprepitant or prior cisplatin treatment. Monitor for CNS toxicity and discontinue ifosfamide treatment for encephalopathy. ▪ Refer to UpToDate topics on "Overview of neurologic complications of conventional non-platinum cancer chemotherapy".

Monitoring parameters:

- CBC with differential and platelet count prior to each new treatment cycle.
- Assess electrolytes (especially potassium, magnesium, and phosphate) and renal function daily during administration and prior to each new treatment cycle.
- Assess liver function tests daily during administration and prior to each new treatment cycle.
- Check urinalysis (or urine dipstick) prior to and during ifosfamide administration to monitor for hemorrhagic cystitis.
- Monitor for ifosfamide-related neurotoxicity (eg, encephalopathy, coma, rarely seizures, weakness, neuropathy, ataxia, cranial nerve dysfunction) daily, on days 2 through 5.
- Refer to UpToDate topic on "Overview of neurologic complications of non-platinum cancer chemotherapy".
- Assess changes in neurologic function, including neuropathy and/or paresthesias, prior to each treatment cycle.
- Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.

Suggested dose modifications for toxicity:

Myelosuppression	▪ **Cycles 2 to 4:** In order to initiate subsequent cycles of therapy, patients must have an ANC ≥0.45 × 10^3 cells/mm^3 and platelet count ≥75 × 10^6 cells/mm^3.[1,6] No dose reductions were allowed in this protocol for hematologic toxicity. However, if patients developed treatment-related

	toxicity, a delay in the next cycle until recovery from the toxicity was allowed, with the next cycle administered at full dose.
Hemorrhagic cystitis	▪ Withhold further ifosfamide and continue the daily mesna if urinalysis shows 10 or more erythrocytes per high-powered field until hematuria is resolved.[4] ▪ Refer to UpToDate topic on "Chemotherapy and radiation-related hemorrhagic cystitis in cancer patients".
Nephrotoxicity	▪ **Cisplatin:** The United States Prescribing Information for cisplatin recommends that the drug be withheld until serum creatinine is <1.5 mg/dL and/or BUN is <25 mg/dL.[3] ▪ **Ifosfamide:** Ifosfamide is associated with cumulative nephrotoxicity and electrolyte abnormalities, mostly at a total dose above 60 g/m^2. Clinical manifestations may include hypophosphatemia, renal potassium wasting, metabolic acidosis with a normal ion gap, and, rarely, polyuria due to nephrogenic diabetes insipidus. ▪ Refer to UpToDate topic on "Ifosfamide nephrotoxicity".
Neurologic toxicity	▪ **Cisplatin:** Neuropathy is usually not seen until cumulative doses of cisplatin >400 mg/m^2, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. ▪ Refer to UpToDate topic on "Overview of neurologic complications of platinum-based chemotherapy". ▪ **Ifosfamide:** CNS toxicities can be severe and result in encephalopathy and death. CNS side effects may be especially problematic for those over age 60. Discontinue ifosfamide treatment for encephalopathy. ▪ Refer to UpToDate topic on "Overview of neurologic complications of non-platinum cancer chemotherapy". ▪ **Paclitaxel:** In cases of severe symptomatic peripheral neuropathy, a dose reduction of 20% is recommended for all subsequent courses of paclitaxel.[5] ▪ Refer to UpToDate topics on "Overview of neurologic complications of conventional non-platinum cancer chemotherapy" and "Prevention and treatment of chemotherapy-induced peripheral neuropathy".
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; RBC: red blood cell count; CNS: central nervous system; CBC: complete blood count; ANC: absolute neutrophil count; BUN: blood urea nitrogen.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ Paclitaxel can be administered in NS, D5W, or NS/D5W* at varying concentrations between 0.3 and 1.2 mg/mL. Use glass or polypropylene bottles or polypropylene or polyolefin plastic bags, and administer through polyethylene-lined administration sets with a microporous membrane 0.22 microns or less.

Δ Due to a longer half-life of ifosfamide and associated metabolites, some references recommend continuation of mesna for 12 to 24 hours beyond completion of ifosfamide to reduce the risk of hemorrhagic cystitis. If necessary, oral mesna may be used at a dose twice that of IV mesna.

◇ The original protocol used a mesna dose of 500 mg/m^2 for each bolus.[1] Alternatively, at some institutions, the total daily mesna dose is initiated 15 minutes prior to ifosfamide infusion and administered continuously over 8 hours.

§ Alternatively, may dilute in 2 L dextrose 5% and sodium chloride 0.45% or dextrose 5% and sodium chloride 0.3% containing 37.5 g of mannitol and infuse over a 6- to 8-hour period.[3]

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1. *Kondagunta GV, et al. J Clin Oncol 2005; 23:6549.*
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Contributor Disclosures

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