Evidence-based Treatment for Advanced Germ Cell Tumor of the Testis With a Case Illustration

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Testicular germ cell tumor is rare in the Asian population. Nevertheless, it is a prototypic cancer of young adults because it can be highly malignant but is also highly curable, even at an advanced stage. We present a case with far-advanced embryonal carcinoma, treated with bleomycin, etoposide and platinum (BEP) × 4 cycles. This case has shown very good results from the treatment. This is the standard therapy for poor- and intermediate-risk patients with germ cell tumors in the advanced stage, supported by current evidence-based literature. BEP × 3 cycles or EP × 4 cycles is the standard therapy for good-risk patients with advanced germ cell tumors. Using these treatments, we can achieve durable remissions of approximately 90%, 75%, and 45% in good-, intermediate-, and poor-risk patients, respectively. However, the physical and psychological long-term outcomes should be carefully monitored. [*J Chin Med Assoc* 2010;73(7):343–352]

Key Words: case illustration, evidence-based management, literature review, testicular germ cell tumor

Introduction

Testicular germ cell tumor (TGCT) is a prototypic cancer of young adults. It can be highly malignant, but is also highly curable (approximately 80%), even at an advanced stage, with modern therapy. TGCT is rare in the Asian population, but is the most common malignancy in adolescent and young adult males aged 15–35 years in Western countries. The age-standardized incidence rate worldwide is approximately 1.5/100,000 with substantial variations between countries.[1] It is more common in Caucasians and its incidence has increased.[2] TGCTs are rare in African and Asian populations, even after migration.[3] Only a few cases have been reported in Taiwan.[4] It has been emphasized that it should be managed by an experienced team. We discuss the experience of TGCTs in the USA and Taiwan and present a case with current evidence-based medicine (EBM) illustration (Table 1). We also discuss how to treat this potentially curable disease.

Case Illustration

A 17-year-old male student visited the genitourinary clinic in early June 2008 due to the new onset of painful swelling of the left scrotum. He was treated with different antibiotics without a response with suspected left epididymitis. The patient had lost 20 kg (89 kg down to 69 kg) in 6 months. Physically, he had swollen left scrotal content with tenderness and local heat without palpable inguinal lymph nodes. Laboratory tests showed negative urinalysis, but there was leukocytosis (12,070/μL). Computed tomography (CT) of the abdomen and pelvis performed on August 22, 2008 showed an enhanced left testicular mass (2.3 cm) with heterogeneous density, multiple left para-aortic and inguinal lymph nodes (the largest was 2 cm), and multiple hepatic tumors in both lobes (the largest was 9 cm) (Figure 1A). Further laboratory tests revealed mild elevation of serum aspartate aminotransferase levels (37 IU/L) and substantial elevations of lactic

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dehydrogenase (LDH) (2,189 IU/L), β-human chorionic gonadotropin (HCG) (26.5 mIU/mL), and α-fetoprotein (AFP) (371 ng/mL) levels (Table 2). Based on the CT findings, left orchiectomy with left inguinal lymph node dissection was performed on August 25, 2008. Pathology showed embryonal carcinoma of the left testis and negative inguinal lymph node involvement.

Medical oncologists started to be involved in the patient's care from August 28, 2008. After reviewing the pathology, we discussed in detail the prognosis, goals of treatment and preparations before chemotherapy with the patient and his family.

Table 1. Different levels of evidence-based medicine applied in this article (from the Oxford Centre for Evidence Based Medicine Levels of Evidence, March 2009)*

Level	Therapy/prevention, etiology/harm
1a	SR (with homogeneity) of RCTs
1b	Individual RCT (with narrow confidence interval)
1c	All or none
2a	SR (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g. <80% follow-up)
2c	"Outcomes" research; ecological studies
3a	SR (with homogeneity) of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

**Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998 and updated by Jeremy Howick in March 2009; freely available from the Oxford Centre for Evidence Based Medicine website (http://www.cebm.net/). SR = systematic review; RCT = randomized controlled trial.*

Preparation

The patient's family had requested 2nd and 3rd opinions from 2 other major tertiary medical centers, and both gave advice similar to ours. Therefore, they decided to stay at our hospital for treatment. We gave them a detailed treatment plan. The patient had a port-A catheter inserted by a general surgeon for future chemotherapy. He also had a pulmonary function test,

Table 2. Serial tumor markers of the case illustration

Date	HCG (mIU/mL) (0–5)	AFP (ng/mL) (0–10)	LDH (IU/L) (95–215)
8–25/08	27	371	2,189
9–10/08	–	–	4,805
9–18/08	279	1,752	3,175
9–22/08	159	961	1,073
9–26/08	–	–	662
10–2/08	–	–	448
10–11/08	–	–	197
10–20/08	<1	14	374
10–26/08	–	6.4	219
11–13/08	<1	3.7	231
2–4/09	<1	2.8	256
3–2/09	<1	2.8	207
4–8/09	<1	3.3	–
5–13/09	<1	2.6	209
6–17/09	<1	2.9	–
7–27/09	<1	2.5	–
9–4/09	<1	2.1	–
10–21/09	<1	2.9	206
12–16/09	<1	2.5	203
1–27/10	<1	2.8	–
3–19/10	<1	3.4	–
5–5/10	<1	2.4	207

HCG = β-human chorionic gonadotropin; AFP = α-fetoprotein; LDH = lactate dehydrogenase.

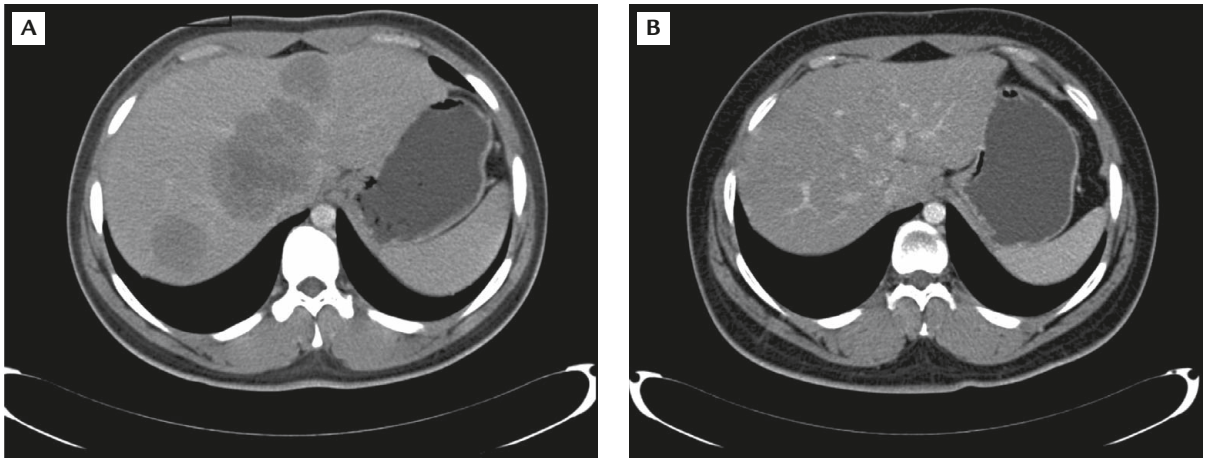

Figure 1. Computed tomography (CT) of the abdomen before and after treatment taken at the same level. (A) Initial CT taken on August 22, 2008 shows multiple liver metastases. (B) Recent CT taken on March 12, 2010 shows improvement.

which revealed normal results before bleomycin treatment.[5] He also had sperm preservation before starting chemotherapy (EBM level 3b).[6]

Staging

The patient's pathology was embryonal carcinoma, one of the nonseminomatous germ cell tumors (NSGCTs) without a teratoma element. During the preparation period, he developed severe lower back pain without evidence of spinal cord compression by neurosurgical evaluation. A bone scan was negative for bone metastasis. He required constant narcotic medication. We believe that this was due to progressive retroperitoneal lymph node enlargement (because his pain subsided after the 1st chemotherapy). His liver was also enlarged, with tenderness on examination. LDH levels were elevated to 4,805 IU/L before the beginning of treatment. In addition, bilateral pulmonary metastases were shown on a CT scan, as well as liver metastases as mentioned above. Therefore, the patient was diagnosed as stage IIIC ($T_2N_1M_{1b}S_3$) (Table 3)[7] and in the poor-risk group (Table 4).[8]

Treatment

We decided to give the patient 4 cycles of bleomycin 30 mg weekly, etoposide 100 mg/m^2 daily × 5 and

Table 3. American Joint Committee on Cancer Clinical staging for testicular germ cell tumors[7]

Tumor (pathological)	
T1	Limited to testis/epididymis without lymphovascular invasion. May invade tunica albuginea but not tunica vaginalis.
T2	Limited to testis/epididymis with lymphovascular invasion or extending to involve tunica vaginalis.
T3	Invades spermatic cord with or without vascular/lymphatic invasion.
T4	Invades scrotum with or without vascular/lymphatic invasion.
Node	
N0	No regional lymph node metastasis.
N1	Lymph node mass ≤ 2 cm in greatest dimension or multiple lymph nodes, none > 2 cm in greatest dimension.
N2	Lymph node mass > 2 cm but not > 5 cm in greatest dimension, or multiple lymph nodes, any 1 mass > 2 cm but not > 5 cm in greatest dimension.
N3	Lymph node mass > 5 cm in greatest dimension.
Metastasis	
M0	No distant metastasis.
M1a	Nonregional lymph node or pulmonary metastasis.
M1b	Distant metastasis other than to nonregional lymph nodes and lungs.
Tumor markers (serum)	
S0	Markers within normal limits.
S1	LDH < 1.5 × N & HCG < 5,000 & AFP < 1,000.
S2	LDH > 1.5–10 N or HCG 5,000–50,000 or AFP 1,000–10,000.
S3	LDH > 10 × N or HCG > 50,000 or AFP > 10,000.
Stage	Extent of disease
Grouping	
I	Confined to the testis (any T, N0, M0).
IA	pT1, N0, M0, S0.
IB	pT2 or pT3 or pT4, N0, M0, S0.
IS	Any T, N0, M0, S1–3.
II	Metastatic disease to the nodes of the periaortic or vena caval zone without pulmonary or visceral involvement (any T, any N 1–3, M0).
IIA	Any T, N1, M0, S0–1.
IIB	Any T, N2, M0, S0–1.
IIC	Any T, N3, M0, S0–1.
III	Metastasis above the diaphragm or involving other viscera or S2–3.
IIIA	Any T, any N, M1a, S0–1.
IIIB	Any T, N1–3, M0–1a, S2.
IIIC	Any T, N1–3, M0, S3; or any T, any N, M1a, S3; or any T, any N, M1b, any S.

N = upper limit of normal for the LDH assay; LDH = lactate dehydrogenase (IU/L); HCG = β-human chorionic gonadotropin (mIU/mL); AFP = α-fetoprotein (ng/mL).

Table 4. Germ cell tumor risk classification[8]

Classification	Seminoma	Nonseminoma
Good risk	Any HCG Any LDH Nonpulmonary visceral Metastasis absent Any primary site	AFP < 1,000 HCG < 5,000 LDH < 1.5 × ULN Nonpulmonary visceral Metastases absent Gonadal or retroperitoneal primary tumor
Intermediate risk	Any HCG Any LDH Nonpulmonary visceral Metastasis present Any primary site	AFP 1,000–10,000 HCG 5,000–50,000 LDH 1.5–10.0 × ULN Nonpulmonary visceral Metastases absent Gonadal or retroperitoneal primary site
Poor risk	Not applicable	AFP ≥ 10,000 HCG ≥ 50,000 LDH ≥ 10 × ULN Mediastinal primary site Nonpulmonary visceral metastases present (e.g. bone, liver, brain)

HCG = β-human chorionic gonadotropin (mIU/mL); AFP = α-fetoprotein (ng/mL); LDH = lactate dehydrogenase (IU/L); ULN = upper limit of normal.

cisplatin 20 mg/m^2 daily × 5 (BEP) due to high-risk stage IIIC (EBM levels 1b[10,12–14] and 2b[11]).[9–14] The chemotherapy began on September 11, 2008 and finished on November 28, 2008, and the patient responded well. He received the full doses on a set schedule[9] with supplement of granulocyte-colony stimulating factor (G-CSF) in all cycles (EBM level 2a).[15] His absolute neutrophil count dropped to 288/μL on day 12 after the 1st cycle of chemotherapy was complicated with acute tonsillitis. All tumor markers returned to normal before the 3rd cycle of chemotherapy (Table 2; EBM levels 2b[17] and 3b[16]).[16,17] Follow-up CT of the chest on October 22, 2008 revealed total disappearance of the pulmonary metastases. The patient's retroperitoneal lymph nodes also regressed in December 2008, but his liver lesions remained in both lobes, with the largest being 2.4 cm. We decided that he could not have post-chemotherapy resection due to multiple lesions in both lobes of the liver (EBM levels 2b,[20] 3a,[21] and 3b[18,19,22]).[18–22] Instead, he underwent CT-guided biopsy of the largest liver lesion, which showed marked tumor necrosis with focal fibrosis.

Problems, intervention, and outcome

The main problem of the presented case was stage IIIC NSGCT belonging to the high-risk group.[7,8] There are many different chemotherapy regimens for TGCT. Based on the above evidence-based literature, our patient received BEP × 4 of the original 5-day regimen (EBM levels 1b[10,12–14,23] and 2b[11]),[9–14,23] without compromising the dose or delaying the schedule. This is the standard treatment for high-risk NSGCT in stage IIIC. He had an excellent response and is still in complete remission according to the latest physical examination, tumor markers (EBM levels 2b[17] and 3b[16])[16,17] (Table 2) and imaging studies (Figure 1B). Another problem was severe neutropenia with acute tonsillitis after the 1st cycle of chemotherapy. This was a complication from the treatment. In general, prophylactic G-CSF is not indicated. In this case, because of the infection with severe neutropenia, the patient received G-CSF in each cycle. He was able to keep his chemotherapy schedule on time and without compromising the dose (EBM level 2a[15]).[9,15] There were no further infectious complications. This was considered to be a successful key point. However, we needed to decide whether the patient should have laparotomy to resect the residual masses shown on CT after 4 cycles of BEP. This is a controversial issue (EBM levels 2b,[20] 3a[21] and 3b[18,19,22]).[18–22,24] His retroperitoneal lymph nodes were nearly gone (< 1 cm) and pulmonary lesions had completely disappeared. The lesions were present in both lobes of the liver, which could not be resected completely unless there was an intention to have a liver transplant. The patient had no teratoma elements in the initial pathology, which made the possibility of teratoma of these residual masses less likely. Therefore, he had CT-guided biopsy to the largest liver lesion instead of laparotomy resection. Other major symptoms and signs were weight loss, severe pain, hepatomegaly and marked elevation of tumor markers. These all resolved after treatment.

Follow-up

The serial follow-up of tumor markers was normal (Table 2). In July 2009, a thymic tumor was suspected from CT of the chest. Video-assisted thoracic surgical resection of the thymus was performed, and the pathology revealed only thymic hyperplasia without evidence of tumor recurrence. CT of the chest, abdomen (Figure 1B) and pelvis revealed no evidence of active disease. The patient is currently in complete remission as shown by normal tumor markers, even though there were residual liver lesions shown on CT that were necrotic, and fibrotic tissue on biopsy. Continued follow-up for relapse and late relapse[25,26] are needed

(EBM level 3b). Long-term complications related to the BEP regimen are also future possibilities (EBM levels 3a[27] and 3b[28–30]).[5,27–30]

Biology, Pathology and Staging

Biology

Recent gene expression profiling studies of TGCTs along with advances in embryonic stem-cell research have contributed to understanding the biology of the disease. Gain of the short arm of chromosome 12 detected in almost all adult germ cell tumors (GCTs) appears to be malfunctional in germ cell tumorigenesis, based on the observed overexpression of genes mapped to this region involved in maintaining pluripotency and oncogenesis.[31]

Pathology

GCTs are classified into 2 broad histological categories: seminomatous and nonseminomatous GCT. Patients with seminoma who have increased AFP levels or any of the NSGCT components (including teratoma) are considered to have a NSGCT. NSGCT is further divided into 4 types as follows.[1] (1) Embryonal carcinoma is composed of large pleomorphic cells with different architectural patterns. It is the most undifferentiated cell type. This tumor may be associated with an elevation of HCG and/or AFP serum levels, as in our case. (2) Endodermal sinus tumor (yolk sac carcinoma) is the most common testicular tumor seen in infants and young children. It is uncommon in the adult testis but accounts for a significant percentage of primary mediastinal NSGCT. It has a variety of architectural patterns. Yolk sac tumor mimics the yolk sac of the embryo, producing AFP. (3) Choriocarcinoma, as a pure entity, is one of the least common GCTs. These tumors have a great propensity for hematogenous spread, often skipping the retroperitoneum. It is associated with an elevated serum level of HCG. (4) Teratoma is generally a benign tumor with elements from 2 or more of the germ layers (ectoderm, mesoderm, and the endoderm). Teratoma is uncommonly seen as the sole histology in primary tumors, but it is frequently associated with other histological elements mentioned above. Serum markers are normal in patients with pure teratoma.

Prognostic classification

GCTs are spread by both lymphatic and vascular channels. Prognosis is related not only to the anatomic extent of the spread but also to the primary site and the extent of production of the tumor markers (EBM level 3b).[32] These features incorporate several prognostic factor classifications of widely differing types and complexity, and it is difficult to compare between different classifications (EBM level 3b).[33] As a result, the International Germ Cell Cancer Collaborative Group (IGCCCG) was formed in 1991. Members agreed to pool clinical data on a large population of patients with metastatic GCT. An agreed prognostic factor classification for use in clinical practice and future trials has resulted from this collaboration. A consensus classification was defined (poor, intermediate, and good) and published in 1997 (Table 4).[8] The American Joint Committee on Cancer adopted this classification in its staging manual beginning from the 6th edition (Table 3).[7]

Clinical Management

Treatment of patients with advanced disease

IGCCCG classification is the only risk assignment algorithm used today in clinical trials and clinical practice. Patients are categorized as good, intermediate, or poor risk and the projected 5-year survival rates are approximately 90%, 75%, and 45%, respectively.[8]

Good-risk GCT

After trials in the late 1970s and early 1980s, the curability of metastatic GCT was established. Strategies were then necessary to decrease the toxicity resulting from therapy. Elimination of bleomycin, substitution of carboplatin for cisplatin, and a reduced number of chemotherapy cycles were studied systematically (EBM level 1b).[34–36] The results of phase 3 randomized trials showed that carboplatin was inferior to cisplatin in combination with etoposide (EBM level 1b).[36,37] In contrast, bleomycin could be eliminated from therapy when 4 cycles of etoposide plus cisplatin had been administered (EBM level 1b).[38] Bleomycin toxicity remains an important issue in good-risk patients.[5] Acute pulmonary toxicity is reduced with BEP × 3 (EBM level 3b[39]).[5,39] Moreover, long-term cardiovascular diseases are now recognized in connection with BEP therapy (EBM level 3b).[28,40] Raynaud's phenomenon is reported to occur in 6–24% of patients (EBM level 1b).[35] Therefore, a randomized trial comparing BEP × 3 with EP × 4 was designed. It was concluded that the regimen of EP × 4 is an alternative to BEP × 3 in good-risk GCT (EBM levels 1b[41] and 3a[42]).[41,42] In addition, the drug dose was determined to be crucial, as survival was superior with an etoposide 500 mg/m^2/cycle compared with a 360 mg/m^2/cycle (EBM level 1b).[38]

Poor- and intermediate-risk GCT

Of patients with metastatic disease, 20–30% appear to be more resistant to initial treatment. Hoping for a better response, double-dose cisplatin and other dose-escalation regimens, as well as alternating and sequential regimens, have been tried, but they did not improve on the standard BEP × 4 (EBM levels 1b[13,14] and 2b[11]).[11,13,14] In a randomized trial comparing BEP × 4 versus VP-16 plus ifosfamide plus platinum (VIP) × 4, the response rates and survival were comparable, but VIP had more hematological toxicity (EBM level 1b).[10] VIP can be offered as an alternative therapy for patients with compromised pulmonary function or other pre-existing conditions precluding treatment with the standard BEP regimen (EBM level 1b).[12] Another randomized trial compared BEP × 4 with BEP × 2 followed by high-dose therapy (carboplatin, etoposide and cyclophosphamide with autologous stem-cell rescue) and showed no difference in outcome (EBM level 1b).[23] Chemotherapy should be given without dose reduction at 21-day intervals. Dose reduction is highly discouraged, even in the setting of a critically-ill patient.[9] Postponing treatment (a maximum of 3 days for each decision) should rarely be considered. For example, in cases of existing fever, with a neutrophil count < 500/μL or platelet counts < 10,000/μL at day 1 of a subsequent cycle,[9] there is no indication for routine prophylactic use of hematopoietic growth factors such as G-CSF (EBM level 2a).[43] However, if serious infections have occurred during 1 preceding chemotherapy cycle, as in the presented case, prophylactic application of G-CSF is recommended in subsequent cycles to maintain the required dose intensity (EBM level 2a).[15] The original 5-day BEP regimen for 4 cycles is standard in intermediate- and poor-risk GCT.[9]

Approximately 10% of all patients with advanced GCT (i.e. 1–2% of all GCTs) present with brain metastases. These patients have a long-term survival of 30–40%, whereas patients who develop brain metastases with other metastases during first-line therapy have a 5-year survival rate of only 2–5% (EBM level 3b).[44]

Monitoring treatment results

Tumor markers and imaging studies are the 2 major tests to monitor the treatment results of GCT (EBM level 2a).[45] The frequency and type of examinations depend on the estimated risk of relapse, the chosen treatment strategy, and the time elapsed since the completion of treatment and should be modified according to their risks. It is important that the markers be measured directly before each treatment cycle, otherwise, the markers can be falsely increased due to release from necrotic tumor cells.[9] A tumor marker (HCG, AFP, and LDH) surge was noted in the very first few weeks after initiation of chemotherapy (EBM level 2b).[17] After the transient elevation, the rate of decline of HCG (half-life, 18–36 hours) and AFP (half-life, 5–7 days) has a prognostic impact on both progression-free survival and overall survival, especially in patients with a poor prognosis, as seen in this case (EBM level 3b[16]).[16,46] After normalization of these markers, they should be followed more frequently at the beginning of treatment and less often later on. The same principle applies to imaging studies. In patients with a slow marker decline or clinical evidence of progression, radiological restaging should be considered (EBM level 3b).[47] The images should include CT of the abdomen and pelvis with contrast and other organs of initial involvement. Positron emission tomography scans are very useful in seminoma patients for residual disease evaluation (EBM level 2b).[48] However, they are not sensitive enough for NSGCT (EBM levels 2b[49] and 3b[50]).[49,50] Progression with tumor markers despite first-line chemotherapy requires the immediate initiation of salvage treatment (EBM levels 2b[17] and 3b[51]).[17,51] Resection of residual masses should be performed in patients with tumor markers persisting at low levels after completion of first-line treatment (EBM level 2b).[52]

Resection of residual tumor

Seminoma

In patients with seminoma, residual masses present after chemotherapy and after radiotherapy should not be resected, but should be closely followed by tumor marker determinations and imaging studies (EBM level 4).[53] Fluorodeoxyglucose-positron emission tomography has a prognostic value in this situation, especially with residual lesions > 3 cm. If the result is negative, no resection or any other treatment is necessary. If the result is positive, histology should be obtained by biopsy or preferably by resection (EBM level 2b).[48] Further treatment should be based on the results of histology and may include observation, radiation, or further chemotherapy (EBM level 3b).[54]

Nonseminoma

Patients with nonseminoma who achieve serologic complete remission (normalization of all tumor markers) will have either complete regression of radiographic abnormalities or persistent radiographic masses. No post-chemotherapy surgery is required in the former situation; there is significant controversy with regard to the latter situation (EBM level 3b).[19] Patients who are initially teratoma-negative and who have more than 90% radiological regression can be followed closely

without resection. However, surgical resection is another option (EBM level 3b).[22] In all other situations, all residual masses should be resected if technically feasible (EBM level 3b[18]).[18,24] Histology of residual masses after first-line chemotherapy shows necrosis (50%), mature teratoma (35%), and vital cancer (15%) (EBM levels 2b[20] and 3a[21]).[20,21] Complete resection of residual teratomas is important because it may progress to obstruct or invade adjacent structures, and is associated with a malignant transformation risk and higher rate of late relapse.[24]

Consolidation chemotherapy after secondary surgery

If the resection histology shows necrosis or teratoma, no further treatment is required. When a viable undifferentiated tumor is found from resection, the role of consolidation chemotherapy is uncertain (EBM level 3b).[18] If > 10% of viable cancer is found, or if completeness of the resection is in doubt, consolidation chemotherapy might be justified.

Salvage chemotherapy for relapsed or refractory disease

In patients who relapse or progress after first-line chemotherapy, prognostic indicators are the localization and histology of the primary tumor, response to first-line treatment, duration of previous remissions, and the levels of tumor markers (EBM level 2b).[55] Caution should be used when suspicion of relapse is based on elevations in tumor markers only. Elevation of AFP can occur from lab errors, hepatoma or liver inflammation. False elevation of HCG may occur in patients who use marijuana, and there is some cross-reactivity in the radioimmunoassay with luteinizing hormone.[56] The common regimens in second- or third-line chemotherapy are paclitaxel plus ifosfamide plus cisplatin (TIP),[57] VIP,[10] vinblastin plus ifosfamide plus cisplatin (VeIP)[58,59] or high-dose chemotherapy.[60,61]

Late relapse

A late relapse is defined as any disease recurrence more than 2 years after completing first-line treatment, and was not recognized before 1983. A pooled analysis of a large series published between 1989 and 2006 showed a crude incidence of 3.2% for nonseminoma and 1.4% for seminoma (EBM levels 3a[25] and 3b[26]).[25,26,62] The most important observation on late relapse in patients who have received cisplatin-based combination chemotherapy is that surgical resection of all recurrent disease is important in determining outcome. This is due to relative resistance to chemotherapy, but is also due to the frequency of teratoma within the recurrence (EBM levels 3a[25] and 3b[26]).[25,26,62] If the lesions are not completely resectable, biopsies should be obtained for histological assessment and salvage chemotherapy should be initiated according to the histological results.

Follow-up, late effects, and psychosocial impact

The aims of follow-up of patients with GCT are detection of relapse, diagnosis of second cancers and their prevention, and treatment of physical and psychological modalities related to GCT or its treatment. Given the long life expectancy of this young patient population, evaluating long-term complications has become increasingly important. First, the risk of a second malignancy has increased; contralateral testicular cancer is highest, between 2–5%, during the first 15 years (EBM level 3b).[63] Other second malignancies are carcinomas in prior radiation fields, and myelodysplasia or leukemia are often associated with etoposide dose (EBM level 3a).[27,64] Cases of leukemia after cumulative doses of etoposide < 2 g have a reported incidence of 0.6%, and incidence is 2% if etoposide dose is ≥ 2 g (EBM level 3a)[64] (our patient received a total of 3,175 mg).

Second, there is the issue of medical late toxicity of chemotherapy. Cisplatin can cause renal dysfunction with a decreasing glomerular filtration rate (EBM level 3b)[65] and high-frequency hearing loss in 20–40% of patients (EBM level 3b).[66] Gonadal dysfunction is common in patients treated with orchiectomy only. Bleomycin can cause pulmonary fibrosis (approximately 5%; EBM level 3b[67])[5,67] and Raynaud's phenomenon (EBM level 3b).[68] The risks of cardiovascular disease (EBM level 3b)[28] and metabolic syndrome (EBM level 3b)[29] are also increased and should be actively monitored.

Third, there are late psychosocial effects among GCT survivors. These include fear of recurrence, survivor guilt, sleep disturbance, cognitive dysfunction, anxiety or depression, difficulty forming relationships, and sexual dysfunction (EBM level 3b).[30,69]

Conclusion

We have presented a case with far-advanced embryonal carcinoma (stage IIIC) treated with current evidence-based therapy that has had very good results. Survival rates with modern therapy in GCT are high. EP × 4 or BEP × 3 is standard therapy for patients with good-risk features, and the cure rate is approximately 90%. Post-chemotherapy resection of all residual masses shown on imaging studies is advised if technically feasible, but there are some controversial issues. BEP × 4 is the standard therapy for intermediate- or

poor-prognosis groups. Approximately 75% of patients in the intermediate-risk group and 45% of patients in the poor-risk group achieve a durable complete remission with these therapies. Patients requiring second- or third-line treatment are managed with TIP, VIP, VeIP, high-dose chemotherapy regimens, or a clinical trial. Finally, with the high rate of survival, quality care must include attention to the long-term outcomes of these young adult patients.

References

1. Bosl GT, Bajorin DF, Sheinfeld J, Motzer RJ, Chaganti RSJ. Cancer of the testis. In: Devita VT Jr, Lawrence TS, Rosenberg SA, eds. *Cancer, Principle and Practice of Oncology*, 8th edition. Philadelphia: Lippincott, Williams & Wilkins, 2008:1464–5.
2. Bray F, Ferlay J, Devesa SS, McGlynn KA, Moller H. Interpreting the international trends in testicular seminoma and nonseminoma incidence. *Nat Clin Pract Urol* 2006;3: 532–43.
3. Oliver R. Epidemiology of testicular cancer. In: Vogelzang NJ, Shipley WU, Scardino PT, Coffey DS, eds. *Comprehensive Textbook of Genitourinary Oncology*, 3rd edition. Philadelphia: Lippincott, Williams & Wilkins, 2006:547–62.
4. Chen YS, Kuo JY, Chin TW, Wei CF, Chen KK, Lin ATL, Chang LS. Prepubertal testicular germ cell tumors: 25-year experience in Taipei Veterans General Hospital. *J Chin Med Assoc* 2008;71:357–61.
5. Azambuja E, Flech JF, Batista RG, Menna Barento SS. Bleomycin lung toxicity: who are the patients with increased risk? *Pulm Pharmocol Ther* 2005;18:363–6.
6. Pont J, Albrecht W. Fertility after chemotherapy for testicular germ cell cancer. *Fertil Steril* 1997;68:1–5.
7. American Joint Committee on Cancer. Testis. In: Greene FL, Page DL, Flemming ID, Fritz AG, Balch CM, Haller DG, Marrow M, eds. *AJCC Cancer Staging Manual*, 6th edition. New York: Springer, 2002:347–54.
8. International Germ Cell Cancer Collaboration Group. International germ cell consensus classification: a prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* 1997;15:594–603.
9. Krege S, Beyer J, Souchon R, Albers P, Albrecht W, Algaba F, Bamberg M, et al. European consensus conference on diagnosis and treatment of germ cell cancer: a report of the second meeting of the European Germ Cell Cancer Consensus Group (EGCCCG): part II. *Eur Urol* 2008;53:497–513.
10. Nichols CR, Catalano PJ, Crawford ED, Vogelzang NJ, Einhorn LH, Loehrer PJ. Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B study. *J Clin Oncol* 1998;16: 1287–93.
11. Kaye SB, Mead GM, Fossa SD, Cullen M, deWit R, Bodrogi I, van Groeningen C, et al. Sequential chemotherapy with BOP/VIP-B compared with treatment with BEP/EP for poor-prognosis metastatic nonseminomatous germ cell tumor: a randomized Medical Research Council/European Organization for Research and Treatment of Cancer study. *J Clin Oncol* 1998; 16:692–701.
12. Hinton S, Catalano PJ, Einhorn LH, Nichols CR, Crawford ED, Volgelzang N, Trump D, et al. Cisplatin, etoposide and either bleomycin or ifosfamide in the treatment of disseminated germ cell tumors: final analysis of an intergroup trial. *Cancer* 2003; 97:1869–75.
13. Nichols CR, Williams SD, Loehrer PJ, Greco FA, Crawford ED, Weetlaufer J, Miller ME, et al. Randomized study of cisplatin dose intensity in poor-risk germ cell tumor: a Southwestern Cancer Study Group and Southwest Oncology Group protocol. *J Clin Oncol* 1991;9:1163–72.
14. DeWit R, Stoter G, Sleijfer DT, Kaye SB, de Mulder PH, ten Bokkel Huinink WW, Spaander PJ, et al. Four cycles of BEP versus alternating regimen of PVB and BEP in patients with poor-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. *Br J Cancer* 1995;71:1311–4.
15. Fossa SD, Kaye SB, Mead GM, Cullen M, de Wit R, Bodrogi I, van Groeningen CJ, et al. Filgrastim during combination chemotherapy of patients with poor prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genitourinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, UK. *J Clin Oncol* 1998;16:716–24.
16. Fizazi K, Culine S, Kramar A, Amato R, Bouzy J, Chen I, Droz JP, et al. Early predicted time to normalization of tumor markers predicts outcome in poor-prognosis nonseminomatous germ cell tumors. *J Clin Oncol* 2004;22:3868–76.
17. DeWit R, Collette L, Sylvester R, de Mulder PH, Sleijfer DT, ten Bokkel Huinink WW, Kaye SB, et al. Serum alpha-fetoprotein surge after the initiation of chemotherapy for non-seminomatous testicular cancer has an adverse prognostic significance. *Br J Cancer* 1998;78:1350–5.
18. Fizazi K, Tjulandin S, Salvioni R, Germa-Lich JR, Bonzy J, Ragan D, Bokemeyer C, et al. Viable malignant cells after primary chemotherapy for disseminated nonseminomatous germ cell tumors: prognostic factors and role of postsurgery chemotherapy: results from an international study group. *J Clin Oncol* 2001; 19:2647–57.
19. Toner GC, Panicek DM, Heelan RT, Geller NL, Lin SY, Bajorin DF, Motzer RJ, et al. Adjunctive surgery after chemotherapy for nonseminomatous germ cell tumors: recommendations for patient selection. *J Clin Oncol* 1990;8:1683–94.
20. Steyerberg EW, Keizer HJ, Fossa SD, Sleijfer DT, Toner GC, Koops HS, Mulders PF, et al. Prediction of residual retroperitoneal mass histology after chemotherapy for metastatic nonseminomatous germ cell tumors: multivariate analysis of individual patient data from six study group. *J Clin Oncol* 1995;13:1177–87.
21. Vergouwe Y, Steyerberg EW, Foster R, Sleijfer DT, Fossa SD, Gerl A, de Wit R, et al. Predicting retroperitoneal histology in postchemotherapy testicular germ cell cancer: a model update and multicentre with more than 1000 patients. *Eur Urol* 2007; 51:424–32.
22. Debono DJ, Heilman DK, Einhorn LH, Donahue JP. Decision analysis for avoiding postchemotherapy surgery in patients with disseminated nonseminomatous germ cell tumors. *J Clin Oncol* 1997;15:1455–64.
23. Motzer RJ, Nichols CJ, Margolin KA, Bacik J, Richardson PG, Volgelzang NJ, Bajorin DF, et al. Phase III randomized trial of conventional-dose chemotherapy with or without high-dose chemotherapy and autologous hematopoietic stem cell rescue as first-line treatment for patients with poor-prognosis metastatic germ cell tumors. *J Clin Oncol* 2007;3:247–56.
24. Stephenson AJ, Sheinfeld J. The role of retroperitoneal lymph node dissection in the management of testicular cancer. *Urol Oncol* 2004;22:225–35.
25. Ronnen E, Kondagunta V, Bacik J, Marion S, Bajorin D, Sheinfeld J, Bosl GJ, et al. Incidence of late relapse germ cell

tumors and outcome to salvage chemotherapy. *J Clin Oncol* 2005;28:6999–7004.
26. Oldengurg J, Alfsen GC, Waehre H, Fossa SD. Late recurrences of germ cell malignancies: a population-based experience over three decades. *Br J Cancer* 2006;94:820–7.
27. Travis LB, Fossa SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, Hall P, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst* 2005;97:1354–65.
28. Van den Belt-Dusebout AW, Nuver J, de Wit R, Gietema JA, ten Bokkel Huinink WW, Rodrigus PTR, Schimmel EC, et al. Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. *J Clin Oncol* 2006;24:467–75.
29. Haugnes HS, Aass N, Fossa SD, Dahl O, Klepp O, Wist EA, Svartberg J, et al. Components of the metabolic syndrome in long-term survivors of testicular cancer. *Ann Oncol* 2007;18: 241–8.
30. Gritz ER, Wellisch DK, Landsverk JA. Psychosocial sequelae in long-term survivors of testicular cancer. *J Psychosoc Oncol* 1988; 6:41–63.
31. Murty VV, Montgomery K, Dutta S, Bala S, Renault B, Bosl GJ, Kucherlapati R, et al. A 3-Mb high-resolution BAC/PAC contig of 12q22 encompassing the 830-Kb consensus minimal deletion in male germ cell tumors. *Genome Res* 1999;9: 662–71.
32. Bajorin DF, Katz A, Chan E, Geller N, Vogelzang N, Bosl GJ. Comparison of criteria for assigning germ cell tumor patients to "good risk" and "poor risk" studies. *J Clin Oncol* 1998;6: 786–92.
33. Mead GM, Stenning SP, Parkinson MC, Horwich A, Fossa SD, Wilkinson PM, Kaye SB, et al. The second Medical Research Council study of prognostic factors in nonseminomatous germ cell tumors. *J Clin Oncol* 1992;10:85–94.
34. Einhorn LH, Williams SD, Loehrer PJ, Birch R, Drasga R, Omura G, Greco FA. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southwestern Cancer Study Group protocol. *J Clin Oncol* 1989;7:387–91.
35. De Wit R, Stoter G, Kaye SB, Sleijfer DT, Jones WG, ten Bokkel Huinink WW, Rea LA, et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular nonseminoma: a randomized study of European Organization for Research and Treatment of Cancer Genitourinary Cancer Cooperative Group. *J Clin Oncol* 1997;15:1837–43.
36. Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, Mead GM, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell tumors: a multi-institutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol* 1997;15:1844–52.
37. Bajorin DF, Sarosdy MF, Pfister DG, Mazumdar M, Motzer RJ, Scher HI, Geller NL, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multiinstitutional study. *J Clin Oncol* 1993;11:598–606.
38. Toner GC, Stochler MR, Boyer MJ, Jones M, Thomson DB, Harvey VJ, Olver IN, et al. Comparison of two standard chemotherapy regimens for good-prognosis germ cell tumors: a randomized trial—Australian and New Zealand Germ Cell Trial Group. *Lancet* 2001;357:739–45.
39. Baniel J, Foster RS, Rowland RG, Bihrle R, Donohue JP. Complications of post-chemotherapy retroperitoneal lymph node dissection. *J Urol* 1995;153:976–80.
40. Huddart RA, Norman A, Shanhidi M, Horwich A, Coward D, Nicholls J, Dearnaley DP. Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol* 2003;21:1513–23.
41. Culine S, Kebrat P, Kramar A, Theodore C, Chevreau C, Geoffrois L, Bui NB, et al. Refining the optimal chemotherapy regimen for good-risk metastatic non-seminomatous germ cell tumors: a randomized trial of the genitourinary group of the French Federation of Cancer Centers (GETUG T39 BP). *Ann Oncol* 2007;18:917–24.
42. Xiao H, Mazumdar M, Bajorin DF, Sarosdy M, Vlamis V, Spicer J, Ferrara J, et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. *J Clin Oncol* 1997;15:2553–8.
43. Bokemeyer C, Kuczyk MA, Kohne H, Einsele H, Kynast B, Schmoll HJ. Hematopoietic growth factors and treatment of testicular cancer: biological interactions, routine use and dose intensive chemotherapy. *Ann Hematol* 1996;72:1–9.
44. Fossa SD, Bokemeyer C, Gerl A, Culine S, Jones WG, Mead GM, Germa-Luch JR, et al. Treatment outcome of patients with brain metastases from malignant germ cell tumors. *Cancer* 1999;85:988–97.
45. Segal R. Surveillance programs for stage I nonseminomatous germ cell tumors of the testis. *Urol Oncol* 2006;24:68–74.
46. Groll RJ, Warde P, Jewett MAS. A comprehensive systematic review of testicular germ cell tumor surveillance. *Crit Rev Oncol Hematol* 2007;64:182–97.
47. Mazumdars M, Bajorin DF, Bacik J, Higgins G, Motzer RJ, Bosl GJ. Predicting outcome to chemotherapy in patients with germ cell tumors: the value of the rate of decline of human chorionic gonadotropin and alpha-fetoprotein during therapy. *J Clin Oncol* 2001;19:2534–41.
48. DeSantis M, Becherer A, Bokemeyer C, Stoiber F, Oechsle K, Sellner F, Lang A, et al. 2-18 Fluorodeoxy-D-glucose positron emission tomography is a reliable predictor for viable tumor in postchemotherapy seminoma: an update of the prospective multicenter SEMPET trial. *J Clin Oncol* 2004;22:1034–9.
49. Huddart RA, O'Doherty MJ, Padhani A, Rustin GJS, Mead GM, Joffe JK, Vasey P, et al. 18 Fluorodeoxyglucose positron emission tomography in the prediction of relapse in patients with high-risk, clinical stage I nonseminomatous germ cell tumors: preliminary report of MRC trial TE 22—the NCRI testis Tumor Clinical Study Group. *J Clin Oncol* 2007;25:3090–5.
50. Oechsle K, Hartmann M, Brenner W, Venz S, Weissbach L, Franzius C, Kliesch S, et al. [18F] Fluorodeoxyglucose positron emission tomography in nonseminomatous germ cell tumors after chemotherapy: the German Multicenter Positron Emission Tomography Study Group. *J Clin Oncol* 2008;26: 5930–5.
51. Zon RT, Nichol C, Einhorn LH. Management strategies and outcomes of germ cell tumor patients with very high human chorionic gonadotropin levels. *J Clin Oncol* 1998;16:1294–7.
52. Kamat MR, Kulkarni JN, Tongoankar HB, Ravi R. Value of retroperitoneal lymph node dissection in advanced testicular seminoma. *J Surg Oncol* 1992;51:65–7.
53. Puc H, Heelan R, Mazumdar M, Herr H, Scheinfeld J, Vlamis V, Bajorin DF, et al. Management of residual mass in advanced seminoma: results and recommendations from Memorial Sloan-Kettering Cancer Center. *J Clin Oncol* 1996;14:454–60.
54. Heidenreich A, Pfister D, Witthuhn R, Thuer D, Albers P. Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. *Eur Urol* 2009;55:217–26.
55. Fossa SD, Stenning SP, Gerl A, Horwich A, Clark PI, Wilkinson PM, Jones WG, et al. Prognostic factors in patients progressing after cisplatin-based chemotherapy for malignant non-seminomatous germ cell tumours. *Br J Cancer* 1999;80: 1392–9.

56. Hayes-Lattin B, Nichols CR. Testicular cancer: a protypic tumor of young adults. *Semin Oncol* 2009;36:432–8.
57. Motzer RJ, Sheinfeld J, Mazumdar M, Bains M, Mariani T, Bacik J, Bajorin D, et al. Paclitaxel, ifosfamide, and cisplatin second-line therapy for patients with relapsed testicular germ cell cancer. *J Clin Oncol* 2000;18:2413–8.
58. Miller KD, Loehrer PJ, Gonin R, Einhorn LH. Salvage chemotherapy with vinblastin, ifosfamide, and cisplatin in recurrent seminoma. *J Clin Oncol* 1997;15:1427–31.
59. Loehrer PJ Sr, Gonin R, Nichols CR, Weathers T, Einhorn LH. Vinblastin plus ifosfamide, plus cisplatin as initial salvage therapy in recurrent germ cell tumor. *J Clin Oncol* 1998;16:2500–4.
60. Pico JL, Rosti G, Kramar A, Wandt H, Koza V, Salvioni R, Theodore C, et al. A randomized trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumors. *Ann Oncol* 2005;16:1152–9.
61. Rick O, Bokemeyer C, Beyer J, Hartmann JT, Schwella N, Kingreen D, Neureither S, et al. Salvage treatment with paclitaxel, ifosfamide, and cisplatin plus high-dose carboplatin, etoposide, and thiotepa followed by autologous stem-cell rescue in patients with relapsed or refractory germ cell cancer. *J Clin Oncol* 2001;19:81–8.
62. Oldenburg J, Martin JM, Fossa SD. Late relapses of germ cell malignancies: incidence, management, and prognosis. *J Clin Oncol* 2006;24:5503–11.
63. Fossa SD, Chen J, Schonfeld SJ, McGlynn KA, McMaster ML, Gail MH, Travis LB. Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men. *J Natl Cancer Inst* 2005;97:1056–66.
64. Wierechy J, Kollmannsberger C, Boehlke I, Kuczyk M, Schleicher J, Schleucher N, Metner B, et al. Secondary leukemia after first-line high-dose chemotherapy for patients with advanced germ cell cancer. *J Cancer Res Clin Oncol* 2005; 131:255–60.
65. Fossa SD, Aass N, Winderen M, Bormer OP, Olsen DR. Long-term renal function after treatment for malignant germ-cell tumours. *Ann Oncol* 2002;13:222–8.
66. Reddel RR, Kefford RF, Grant JM, Coates AS, Fox RM, Tattersall MH. Ototoxicity in patients receiving cisplatin: importance of dose and method of drug administration. *Cancer Treat Rep* 1982;66:19–23.
67. Haugnes HS, Aass N, Fossa SD, Dahl O, Brydoy M, Ausebo U, Wilsgaard T, et al. Pulmonary function in long-term survivors of testicular cancer. *J Clin Oncol* 2009;27:2779–86.
68. Nicholas J, Vogelsang NJ, Bosl GJ, Johnson K, Kennedy BJ. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. *Ann Intern Med* 1981;3: 288–92.
69. Gritz ER, Wellisch DK, Wang HJ, Siau J, Landsverk JA, Cosgrove MD. Long-term effects of testicular cancer on sexual functioning in married couples. *Cancer* 1989;64:1560–7.