Testicular Cancer Update

Nabil Adra, MD, and Lawrence H. Einhorn, MD

Dr Adra is a fellow in the division of hematology/oncology and Dr Einhorn is Indiana University Distinguished Professor of Medicine and Livestrong Foundation Professor of Oncology at the Indiana University School of Medicine and Melvin and Bren Simon Cancer Center in Indianapolis, Indiana.

Corresponding author:
Nabil Adra, MD
535 Barnhill Drive, RT 400
Indianapolis, IN 46202
Tel: (317) 220-7786
Fax: (317) 948-9302
E-mail: nadra@iu.edu

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Abstract: The advances seen in the treatment of testicular cancer are among the great achievements in modern medicine. These advances were made possible by the collaborative efforts of cancer researchers around the world. Investigators have been able to address many questions regarding the treatment of patients with disease limited to the testis, those with metastasis to the retroperitoneum only, and those with advanced metastatic disease. Questions answered include the chemotherapeutic agents to be used and in what combinations, the proper intensity of treatment and appropriate dosing, the optimal number of cycles of chemotherapy according to validated risk stratification, appropriate surgical approaches that preserve sexual function, the treatment of relapsed disease, what supportive care measures to take, and survivorship issues following treatment of testicular cancer. Today, cure is achievable in 95% of all patients with testicular cancer and 80% of those who have metastatic disease. Despite remarkable results with frontline and salvage combination chemotherapy, metastatic testicular cancer remains incurable in approximately 10% of patients, and novel treatment approaches are warranted. This review highlights past and recent discoveries in the treatment of patients with testicular cancer.

Introduction

Testicular cancer is the most common cancer diagnosis in men aged 15 to 35 years, and the incidence has risen over the past several decades.[1] An estimated 8850 cases of testicular cancer are diagnosed annually in the United States.[2] Germ cell tumors account for the vast majority (95%) of cases of testicular cancer, with other testicular neoplasms (sex cord–stromal tumors, lymphoma) occurring rarely. Germ cell tumors also may arise in extragonadal locations, including the retroperitoneum and the mediastinum.

Substantial advances have been made in the treatment of testicular cancer, and these have been among the great achievements in modern medicine. The introduction and refinement of cisplatin-based combination chemotherapy revolutionized the treatment of testicular cancer. Testicular cancer, which once carried a dismal prognosis, is now curable, even in patients with metastatic disease,[3-6] so that this disease has become a model for transforming a once-fatal

neoplasm into one that can be cured. This review highlights past and present discoveries in testicular cancer and emphasizes areas for further investigation.

Pathogenesis and Epidemiology

Germ cell tumors are malignancies of the primordial germ cells, which are the cells that become spermatozoa. As neoplastic transformation occurs, these cells acquire various histologic features. This process reflects the broad differentiation capabilities of germ cells. The first tumorigenic event leading to the development of germ cell tumors occurs in utero and produces the precursor lesion, termed *intratubular germ cell neoplasia*.[7,8] In adults, this premalignant entity precedes both seminomas and nonseminomatous germ cell tumors. Intratubular germ cell neoplasia is present in testicular tissue adjacent to germ cell tumors in approximately 90% of adult cases,[9] and individuals with intratubular germ cell neoplasia have a 50% risk for the development of testicular cancer within 5 years.[10] Intratubular germ cell neoplasia is derived from gonocytes that have failed to differentiate into spermatogonia and that remain quiescent from the initial insult in utero until hormonal changes occur during puberty.

Testicular germ cell tumors are broadly separated into 2 groups: seminomas and nonseminomas, each accounting for approximately 50% of cases. These 2 tumor groups differ in pathogenesis, histology, clinical course, and response to therapy. Seminomas consist of transformed germ cells that resemble gonocytes but have a differentiation block. Nonseminomas consist of several histologic subtypes, including embryonal carcinoma, choriocarcinoma, yolk sac tumor, and teratoma. Embryonal carcinoma cell lines resemble undifferentiated stem cells, and their patterns of gene expression resemble those of intratubular germ cell neoplasia.[11,12] Choriocarcinomas and yolk sac tumors have extraembryonic differentiation, and teratomas have somatic differentiation.

Several candidate genetic loci have been identified as contributors to the pathogenesis of testicular cancer.[13-15] Germ cell tumors are characterized by the acquisition of extra copies of chromosome 12p. This occurs most commonly through an isochromosome (i12p).[16,17] Chromosome 12q21 contains genes encoding proteins involved in KIT ligand (KITLG)/KIT signaling.[18] It has been postulated that the development of intratubular germ cell neoplasia may involve aberrantly activated KITLG/KIT in utero, which induces the arrest of embryonic germ cells at the gonocyte stage; subsequently, overexpression of embryonic transcription factors such as NANOG, sex-determining region Y–box 17 (SOX17), and octamer-binding transcription factor 3/4 (OCT3/4, also known as POU domain, class 5, transcription factor 1 [POU5F1]) leads to the suppression of apoptosis, increased proliferation, and the accumulation of mutations in gonocytes.[19]

Single gene mutations are uncommon in testicular cancer. *KIT, TP53, KRAS/NRAS,* and *BRAF* are the genes that are most commonly mutated in germ cell tumors and are implicated in their pathogenesis. Different histologic subtypes possess specific gene expression profiles that reflect variations in differentiation.

It is postulated that the distinct gene expression profiles of germ cell tumors are achieved through differential epigenetic regulation, in particular DNA methylation.[20] Gonocytes have almost completely demethylated DNA, and this facilitates the accumulation of mutations during cell replication and is implicated in the development of intratubular germ cell neoplasia and germ cell tumors thereafter.

Worldwide, testicular cancer accounts for approximately 72,000 diagnoses and 9000 deaths per year.[21] Epidemiologic studies suggest that the incidence of testicular cancer has been rising since the early 1900s.[22-26] Genetic and environmental factors, both in utero and during childhood, have been proposed to be responsible for this increased incidence, which has been observed only in white males. Testicular cancer is less common in African Americans, with the incidence among African Americans estimated to be one-fourth that in whites.[27]

The risk for testicular cancer is increased 8- to 10-fold in the brother of a person with testicular cancer and 4- to 6-fold in the son of a person with testicular cancer.[28] Cryptorchidism occurs in up to 5% of boys born at term and is the best-characterized risk factor for testicular cancer.[29] The timing of orchiopexy influences the risk for testicular cancer. In a cohort study conducted in Sweden between 1964 and 1999, a total of 16,983 men who were surgically treated for an undescended testis were followed for 209,984 person-years. The relative risk for testicular cancer among those who underwent orchiopexy before age 13 years was 2.23, whereas it was 5.4 in those who underwent orchiopexy at 13 years or older. This finding suggests that hormonal changes at puberty have a role in the development of testicular cancer. Most patients with a diagnosis of testicular cancer, however, do not have a history of cryptorchidism. A personal history of testicular cancer in the contralateral testis confers an approximately 2% risk for a second primary testicular neoplasm.[30]

Clinical Presentation and Diagnosis

In most patients, testicular cancer is diagnosed when it is still limited to the testes (stage I). The typical presentation is a painless nodule or swelling noted by the patient or his partner. Less commonly, patients present with pain in the scrotal area or with gynecomastia. A minority of patients

present with symptoms related to metastatic disease in the retroperitoneum (stage II), such as back pain, or related to metastatic disease beyond the retroperitoneal lymph nodes (stage III), such as cough, hemoptysis, chest pain, and headaches. Some patients also present with painless supraclavicular lymph nodes.

Scrotal ultrasonography revealing a hypoechoic mass is diagnostic of testicular cancer. A trans-scrotal testicular biopsy should not be attempted, given concern for contamination of the scrotum and alteration of the lymphatic drainage of the tumor. Staging for testicular cancer is critical; stage should be determined with computed tomography (CT) of the chest, abdomen, and pelvis and measurement of the levels of tumor markers for germ cell tumors, including α-fetoprotein (AFP) and human chorionic gonadotropin (hCG). The lactate dehydrogenase (LDH) level should be checked only on the day that chemotherapy is initiated because this can be an indicator of the bulk of disease but is not independently used as a tumor marker or prognostic criterion.

When a patient presents with a suspicious testicular mass that is confirmed on ultrasonography, a radical inguinal orchiectomy is both diagnostic and therapeutic. Pathologic interpretation of the tumor sample should include the size, histologic composition (including the percentage of each histologic subtype present in the tumor sample), and presence or absence of lymphovascular invasion and rete testis invasion.

Stage I Testicular Cancer

Seminoma

Clinical stage I seminoma is usually cured with orchiectomy alone. Adjuvant radiotherapy was an option for many years, but this practice changed after the introduction of effective chemotherapy. After orchiectomy, options for patients with clinical stage I seminoma include active surveillance, radiation therapy to the para-aortic lymph nodes, or a single dose of carboplatin dosed at an area under the curve (AUC) of 7. Most patients today elect for active surveillance, given the low chance of disease recurrence. If radiotherapy is the choice, 20 Gy is delivered to the ipsilateral retroperitoneal lymph nodes. If the patient has a history of prior surgery in the inguinal, pelvic, or scrotal area, then the radiation field is expanded to include the inguinal lymph nodes. The risk for relapse is higher with active surveillance (20%) than with chemotherapy or radiation therapy (4%), but the long-term survival is approximately 99% irrespective of the initial treatment chosen by the patient.[31-33] Risk factors for relapse in clinical stage I seminoma include rete testis involvement and a primary tumor larger than 4 cm.[34] In a Danish population-based study of 1954 patients, there were 369 relapses (19%). Disease-specific survival at the median follow-up of 15 years was 99%.[33] At our institution, the surveillance regimen consists of history and physical examination; measurement of tumor markers, including AFP and hCG; and CT of the abdomen every 4 months during the first year, every 6 months during the second year, and then annually during the third, fourth, and fifth years of follow-up. If a patient has history of pelvic, inguinal, or other surgery that would have altered the lymphatic drainage, CT of the abdomen and pelvis is obtained for surveillance.

Nonseminoma

For patients with stage I nonseminomatous germ cell tumors, options after orchiectomy include active surveillance, nerve-sparing retroperitoneal lymph node dissection, and adjuvant chemotherapy with bleomycin/etoposide/cisplatin (BEP) for 1 cycle. Several studies have indicated that the long-term cure rate with any of these options is 99%.[35-39] Risk factors for relapse in patients with clinical stage I nonseminoma include lymphovascular invasion and embryonal carcinoma as the predominant histology in the primary tumor.[35,40] The risk for relapse in patients who have no risk factors is approximately 15% with surveillance; this rate increases to approximately 50% with surveillance in the presence of risk factors. In a large retrospective study of 1139 patients with clinical stage I nonseminoma, the cure rate was 99% in all patients irrespective of their initial risk factors for relapse or choice of treatment after orchiectomy.[35] Moreover, the vast majority of relapses occurred within 2 years after orchiectomy. The preference at our institution is for active surveillance in nearly all patients who are able to adhere to the close follow-up schedule. We recommend a surveillance program with history and physical examination and measurement of tumor markers (AFP and hCG) every 2 months during the first year, every 6 months during the second year, and annually during years 3, 4, and 5 of follow-up. Imaging should include chest radiography and CT of the abdomen every 4 months during the first year, every 6 months during the second year, and annually during years 3, 4, and 5 of follow-up. If a patient has a history of pelvic, inguinal, or other surgery that would have altered the lymphatic drainage, then CT of the abdomen and pelvis is obtained for surveillance. There are complicated arguments for and against any of the 3 options for the management of clinical stage I testicular cancer, and these are summarized in Table 1.

Stage II Testicular Cancer

Seminoma

Patients with stage II seminoma have metastatic disease

Table 1. Treatment Options for Clinical Stage I Testicular Cancer

Option	Outcomes	Pros	Cons	References
Seminoma				
Active surveillance	• Relapse rate, 20% • Cancer-specific survival, 99%	• Most men spared treatment • Long-term outcomes excellent even in patients with relapse	• Many physician visits • Life disruption if relapse	• Mortensen et al[33] • Soper et al[32] • Oldenburg et al[39]
Radiotherapy	• Relapse rate, 4% • Cancer-specific survival, 99%	• Reduces risk for relapse • Reduces risk for requiring chemotherapy • Reduces frequency of need for abdominal imaging	• Short-term side effects • Long-term risk for secondary cancer	• Soper et al[32] • Oldenburg et al[39] • Oliver et al[31]
Carboplatin (1 or 2 cycles)	• Relapse rate, 4% • Cancer-specific survival, 99%	• Reduces risk for relapse • Reduces risk for requiring chemotherapy	• Short-term side effects of carboplatin • Long-term risks of carboplatin unknown	• Oldenburg et al[39] • Oliver et al[31]
Nonseminoma				
Active surveillance	• Relapse rate overall, 30% • Relapse rate if no risk factors, 15% • Relapse rate in high-risk group with risk factors, 50% • Cancer-specific survival, 99%	• Most men spared treatment • Long-term outcomes excellent even in patients with relapse	• Many physician visits • Life disruption if relapse	• Kollmannsberger et al[35] • Schmoll et al[36] • Tandstad et al[34]
Retroperitoneal lymph node dissection	• Relapse rate, 20%-30% • Cancer-specific survival, 99%	• Cures some patients with pathologic stage II disease • Avoids need for chemotherapy in some patients • No recurrence of disease in retroperitoneum	• Surgical risk • In most patients, normal pathology findings in retroperitoneal lymph nodes • Chemotherapy possibly required if relapse	• Schmoll et al[36] • Albers et al[37]
Bleomycin, etoposide, cisplatin (1 cycle)	• Relapse rate, 1%-5% • Cancer-specific survival, 99%	• Reduces risk for requiring longer course of chemotherapy	• Early toxicity • Overtreatment in substantial number of patients • Long-term risk of 1 or 2 cycles of chemotherapy unknown	• Schmoll et al[36] • Tandstad et al[34] • Albers et al[37] • Westermann et al[38]

confined to the retroperitoneal lymph nodes. Low-volume stage II disease, defined by lymph nodes no greater than 3 cm in diameter, can be treated with 30 to 36 Gy of radiation to the para-aortic and ipsilateral iliac lymph nodes.[39] For all other patients, the preferred therapy is 3 courses of combination chemotherapy with BEP or 4 courses of etoposide/cisplatin (EP).[41] With cisplatin-based combination chemotherapy, cures are achieved in 98% of patients. Patients who have bulky stage II disease should not undergo radiotherapy, which is associated with a high relapse rate in these patients.[42] Treatment options for patients with stage II disease are summarized in Table 2.

Post-treatment residual masses can be challenging to interpret in patients with seminoma. They usually represent desmoplastic changes; surgical resection of these residual masses only rarely shows residual seminoma and can be quite challenging. We typically observe patients with residual masses smaller than 3 cm in diameter following treatment. Masses larger than 3 cm have a higher likelihood of containing residual viable seminoma. In these cases, positron emission tomography (PET) performed

Table 2. Treatment of Clinical Stage II Testicular Cancer

Option	Indication	Outcomes	References
Seminoma			
Radiotherapy (30-36 Gy to para-aortic and ipsilateral iliac lymph nodes)	Nonbulky disease (<3 cm)	5-y OS, 97%	• Domont et al[42] • Schmoll et al[41]
Chemotherapy (BEP × 3 or EP × 4)	Bulky disease (>3 cm)	5-y OS, 98%	• Domont et al[42] • Schmoll et al[41]
Nonseminoma			
Retroperitoneal lymph node dissection	Nonbulky disease (<3 cm)	5-y OS, 98%	• Donohue et al[44] • Schmoll et al[36]
Chemotherapy (BEP × 3 or EP × 4)	Bulky disease (>3 cm)	5-y OS, 98%	• Schmoll et al[36]

BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; OS, overall survival; y, year.

6 weeks after the completion of therapy can assist in making the decision whether surgical intervention is needed to resect residual retroperitoneal masses.[43]

A phase 2 clinical trial is currently evaluating retroperitoneal lymph node dissection as the primary treatment in patients with stage II seminoma and nonbulky disease (NCT02537548).

Nonseminoma

Patients with low-volume stage II nonseminomatous germ cell tumors have metastatic disease confined to the retroperitoneal lymph nodes, lymph nodes no larger than 3 cm, and normal tumor marker levels (AFP and hCG) following orchiectomy. These patients are typically treated with retroperitoneal lymph node dissection.[44] At our institution, patients with high-volume stage II disease or increasing levels of tumor markers (AFP or hCG) are treated with chemotherapy consisting of 3 cycles of BEP or 4 cycles of EP. These regimens achieve cures in approximately 95% to 99% of patients with stage II nonseminoma.

Following chemotherapy, patients who have persistently enlarged retroperitoneal lymph nodes with normal tumor marker levels (AFP and hCG) should undergo retroperitoneal lymph node dissection to resect residual tumor and/or teratoma. The management of patients who have stage II nonseminoma with complete serologic and radiographic remission remains unsettled. At our institution, we do not recommend retroperitoneal lymph node dissection if the retroperitoneal lymph nodes have normalized on CT scans. In a retrospective study, 141 patients with nonseminoma in whom complete radiographic and serologic remission was achieved after first-line chemotherapy were followed for a median of 15.5 years with no retroperitoneal lymph node dissection after chemotherapy. The 15-year recurrence-free survival rate was 90%, and the cancer-specific survival rate was 97%.[45] Given the concern for the presence of viable germ cell tumor and/or teratoma in some patients with normal-size lymph nodes after chemotherapy, some investigators recommend retroperitoneal lymph node dissection after chemotherapy in most patients.[46] In a meta-analysis, 1043 patients who had metastatic nonseminoma treated with cisplatin-based chemotherapy were evaluated. Among these, 588 underwent retroperitoneal lymph node dissection after chemotherapy and 455 were followed with surveillance only.[47] In the patients who underwent resection after chemotherapy, the pooled estimates of necrosis, teratoma, and active cancer were 71%, 24%, and 4%, respectively. The pooled estimate of relapse among the patients who were followed after chemotherapy with surveillance alone was 5%, with a rate of relapse in the retroperitoneum only of 3%. Therefore, retroperitoneal lymph node dissection after chemotherapy can be avoided in approximately 95% of patients with radiographic and serologic remission. At our institution, these patients are followed with surveillance.

Stage III Testicular Cancer

The discovery of cisplatin[48] and the refinement of combination chemotherapy revolutionized the treatment of metastatic testicular cancer. In 1974, the addition of cisplatin to a regimen of vinblastine and bleomycin achieved a 5-year survival rate of 64%, which was unprecedented compared with the rates achieved with previous chemotherapy regimen.[4] Cisplatin-based combination chemotherapy regimens were then refined in multiple subsequent studies.[3,5,6] Based on a randomized clinical trial showing improved efficacy and less toxicity, first-line chemotherapy with 4 cycles of BEP became the standard of care for patients with advanced testicular cancer.[6] Investigators

recognized that cumulative toxicity increased with each additional cycle of chemotherapy, and randomized trials in patients with low-risk disease showed that 3 cycles of BEP was noninferior to and achieved outcomes similar to those obtained with 4 cycles of BEP or 3 cycles of BEP plus 1 cycle of EP.[5,49] A randomized clinical trial comparing 3 cycles of BEP vs 4 cycles of EP in patients with low-risk disease favored 3 cycles of BEP (4-year event-free survival rates, 91% and 86%, respectively), although the difference was not statistically significant (P=.14).[50] Our preferred regimen for patients with low-risk metastatic disease is 3 cycles of BEP, but 4 cycles of EP is also considered a standard regimen for these patients. Randomized trials have shown numeric superiority of 3 cycles of BEP over 4 cycles of EP, although the difference was not statistically significant.

After a multinational analysis in 1997, the International Germ Cell Cancer Collaborative Group (IGCCCG) published a consensus statement classifying patients with metastatic germ cell tumors as having good-risk, intermediate-risk, or poor-risk disease based on specified prognostic criteria: primary tumor site, metastatic sites, and amplitude of serum tumor marker levels.[51] This classification was based on an international collaboration that evaluated 5202 patients with metastatic germ cell tumors. For seminoma, good-risk patients were defined as having any primary tumor site, no nonpulmonary visceral metastasis (liver, brain, bone, or other), and any tumor marker levels (hCG, LDH; the AFP level by definition is normal in patients with seminoma); intermediate-risk patients were defined as having nonpulmonary visceral metastasis. For nonseminoma, good-risk patients were defined as having a primary testis or retroperitoneal tumor site, no nonpulmonary visceral metastasis, and good tumor marker levels (AFP <1000 ng/mL, hCG <5000 mIU/mL, LDH <1.5 × upper limit of normal); intermediate-risk patients were defined as having intermediate tumor marker levels (AFP 1000-10,000 ng/mL, hCG 5000-50,000 mIU/mL, LDH 1.5-10 × upper limit of normal); and poor-risk patients were defined as having a mediastinal primary tumor site, nonpulmonary visceral metastasis, or poor tumor marker levels (AFP >10,000 ng/mL, hCG >50,000 mIU/mL, LDH >10 × upper limit of normal).[51] Patients with good-risk germ cell tumors accounted for 60% of all metastatic cases, with a 5-year progression-free survival (PFS) rate of 88% and a 5-year overall survival (OS) rate of 91%. Patients with intermediate-risk germ cell tumors accounted for 26% of all cases, with a 5-year PFS rate of 75% and a 5-year OS rate of 79%. Patients in the poor-risk category accounted for 14% of cases, with a 5-year PFS rate of 41% and a 5-year OS rate of 48%.

With the above risk stratification, the treatment of metastatic testicular cancer has been refined according to the patient's chance of response to first-line chemotherapy and risk for relapse. Patients with good-risk disease are treated with 3 cycles of BEP or 4 cycles of EP and are expected to have a cure rate above 90% with first-line chemotherapy.[3,5,6,49,50] Patients with intermediate-risk disease are treated with 4 cycles of BEP or 4 cycles of etoposide/ifosfamide/cisplatin (VIP) and are expected to have a cure rate of greater than 80% with first-line chemotherapy.[52-54] Patients with poor-risk disease are treated with 4 cycles of BEP or VIP and are expected to have a cure rate of 50% to 60% with first-line chemotherapy.[53,55-59]

The intermediate-risk group is a heterogeneous category with varying outcomes. At our institution, we consider that 4 cycles of BEP or VIP may be overtreatment in some patients with intermediate-risk disease, and we recommend treatment with 3 cycles of BEP followed by 1 cycle of EP in these selected patients. A retrospective analysis did not show any difference between the survival outcomes of the intermediate-risk patients who received treatment with one or the other of these regimens.[60]

Several attempts have been made to intensify first-line therapy in the hope of increasing cure rates among patients with intermediate-risk or poor-risk disease. Unfortunately, these attempts have failed to show any survival advantage over 4 cycles of BEP or VIP. In addition, these intensified regimens increased toxicity in clinical trials.[52,55-57] Some investigators proposed intensification of therapy according to the rate of decline in tumor markers (AFP and hCG) in patients with high-risk disease after the first or second cycle of BEP chemotherapy.[58] This strategy resulted in fewer relapses and appeared to improve OS, albeit at the expense of greater toxicity, compared with the control arm in this study but not compared with contemporary survival outcomes.[59,61]

A novel regimen of paclitaxel/ifosfamide/cisplatin (TIP) was studied in a phase 2 trial that enrolled patients with intermediate-risk or poor-risk germ cell tumors. Results showed a complete response rate of 68% and a partial response rate of 13%.[62] With this regimen, the estimated 3-year PFS and OS rates were 90% and 100%, respectively, for intermediate-risk patients and 63% and 87%, respectively, for poor-risk patients. A randomized phase 2 trial comparing BEP vs TIP as first-line therapy for patients with intermediate-risk or poor-risk germ cell tumors is ongoing (NCT01873326).

Treatment options for patients with stage III disease are summarized in Table 3.

Relapsed Testicular Cancer

The most effective salvage regimen for patients with relapsed testicular cancer remains unsettled. Disease that relapses after initial chemotherapy but is anatomically

Table 3. First-line Treatment of Stage III Testicular Cancer

Treatment	Indication	Outcomes	References
Good-risk disease[a] • *Seminoma*: any primary tumor site + no NPVM + any tumor marker levels (hCG, LDH) • *Nonseminoma*: testis or retroperitoneal primary tumor + no NPVM + good-risk tumor marker levels (AFP <1000 ng/mL, hCG <5000 mIU/mL, LDH <1.5 × upper limit of normal)			
BEP × 3 EP × 4	• For most patients • For patients who must avoid bleomycin (age >50 y, serum Cr >2 mg/dL)	• 5-y PFS, 90% • 5-y OS, 97%	• Bosl et al[3] • Williams et al[6] • Einhorn et al[5] • de Wit et al[49] • Culine et al[50]
Intermediate-risk disease[a] • *Seminoma*: any primary tumor site + NPVM + any tumor marker levels (hCG, LDH) • *Nonseminoma*: testis or retroperitoneal primary + no NPVM + intermediate-risk tumor marker levels (AFP 1000-10,000 ng/mL, hCG 5,000-50,000 mIU/mL, LDH 1.5-10 × upper limit of normal)			
BEP × 4 or VIP × 4 BEP × 3 + EP ×1	• For intermediate-risk patients with high-volume tumor bulk • For intermediate-risk patients with low-volume tumor bulk	• 5-y PFS, 84% • 5-y OS, 93%	• de Wit et al[52] • Nichols et al[53] • Albany et al[60]
Poor-risk disease[a] • *Seminoma*: no poor-risk cases • *Nonseminoma*: mediastinal primary tumor *OR* NPVM *OR* poor-risk tumor marker levels (AFP >10,000 ng/mL, hCG >50,000 mIU/mL, LDH >10 × upper limit of normal)			
BEP × 4 or VIP × 4	• For all patients	• 5-y PFS, 58% • 5-y OS, 73%	• Nichols et al[53] • Motzer et al[55] • Droz et al[56] • Daugaard et al[57] • Fizazi et al[58] • Adra et al[59]

AFP, α-fetoprotein; BEP, bleomycin/etoposide/cisplatin; Cr, creatinine; EP, etoposide/cisplatin; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NPVM, nonpulmonary visceral metastasis; OS, overall survival; PFS, progression-free survival; VIP, etoposide/ifosfamide/cisplatin; y, year.

[a] Risk per IGCCCG (International Germ Cell Cancer Collaborative Group).

confined can still be cured by salvage surgery.[63] The vast majority of patients, however, will be treated with salvage chemotherapy, including standard-dose chemotherapy or high-dose chemotherapy. Second-line standard-dose chemotherapy options include VIP, TIP, and vinblastine/ifosfamide/cisplatin (VeIP).[64-66]

High-dose chemotherapy followed by bone marrow transplant was first investigated at Indiana University in 1986.[67] Bone marrow was replaced by peripheral blood stem cells in 1996. This accelerated engraftment, so there were fewer delays in delivering a second course of high-dose chemotherapy. Among the first 184 patients treated with high-dose chemotherapy and peripheral blood stem cell transplant for germ cell tumors that progressed after first-line or second-line cisplatin-based chemotherapy, cures were achieved in 70% of those in the second-line setting and in 45% of those who were treated in the third-line or a subsequent setting.[68]

In an updated analysis from Indiana University, 364 consecutive patients with relapsed germ cell tumors were treated with high-dose chemotherapy and autologous peripheral blood stem cell transplant between 2004 and 2014.[69] With a median follow-up of 3.3 years, the 2-year PFS rate was 60% and the 2-year OS rate was 66%. A total of 303 patients received high-dose chemotherapy as second-line therapy, with a 2-year PFS rate of 63%, and 61 patients received high-dose chemotherapy as third-line or later therapy, with a 2-year PFS rate of 49%. There were 122 patients with platinum-refractory disease, defined as tumor progression within 4 weeks after platinum-based chemotherapy, with a 2-year PFS rate of 33%. There were 90 patients with seminoma in

this study, with a 2-year PFS rate of 90%. The treatment-related death rate was 2.5%.

Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) pioneered another widely used high-dose chemotherapy regimen. This regimen incorporates paclitaxel/ifosfamide (TI) as induction chemotherapy, and stem cell mobilization is followed by high-dose carboplatin/etoposide (CE) with peripheral blood stem cell transplant for 3 cycles (TI/CE regimen).[70] In a phase 1/2 trial that enrolled 107 patients, the reported 5-year disease-free survival rate was 47% and the OS rate was 52%. The patients who had a satisfactory decline in tumor marker levels during high-dose chemotherapy had superior PFS and OS rates; however, a cure could be achieved even in the patients with an unsatisfactory decline in tumor marker levels.[71]

The choice of initial salvage chemotherapy for relapsed testicular cancer remains controversial. One of the challenges is determining which patients should be treated with salvage standard-dose chemotherapy vs high-dose chemotherapy. A randomized phase 3 study comparing sequential chemotherapy with a single course of high-dose chemotherapy showed superior OS in the arm receiving sequential high-dose chemotherapy.[72] A prospective phase 3 trial did not show a difference in survival in a comparison of VIP for 4 cycles vs VIP for 3 cycles followed by high-dose chemotherapy with CE plus cyclophosphamide for 1 cycle.[73] In 2011, Lorch and colleagues reported outcomes from a large multi-institutional database evaluating 1594 patients with relapsed germ cell tumors.[74] This retrospective study included a diverse patient population stratified to prognostic subgroups according to the International Prognostic Factors Study Group. Patients were treated with heterogeneous salvage chemotherapy regimens between 1990 and 2008. In this study, high-dose chemotherapy achieved superior outcomes compared with standard-dose chemotherapy, and there was an overall 56% decrease in the risk for progression after first salvage treatment favoring high-dose chemotherapy. This translated into a statistically significant improvement in OS with high-dose chemotherapy in all prognostic subgroups except the low-risk group. The superior outcomes with high-dose chemotherapy were more pronounced in patients with intermediate-risk, high-risk, or very high-risk disease.

Studies have indicated that high-risk relapsed disease (eg, platinum-refractory disease, primary mediastinal nonseminoma, progressive brain metastases) can be cured with high-dose chemotherapy.[69,70] Such results are rarely seen with standard-dose chemotherapy in high-risk patients. With high-dose chemotherapy, cure rates are approximately 25% for patients with relapsed primary mediastinal nonseminoma, 40% for patients with progressive brain metastases, and 33% for patients with platinum-refractory disease.[69]

Some investigators advocate the use of high-dose chemotherapy in most patients as the second-line regimen. Other investigators, however, have proposed the use of high-dose chemotherapy only in high-risk patients, those who have had a relapse after receiving ifosfamide-based chemotherapy, and those who have had a relapse after 2 lines of standard salvage therapy. Optimal patient selection for high-dose chemotherapy vs standard-dose chemotherapy as initial salvage is currently being studied in a randomized phase 3 trial as part of an international collaboration called TIGER (Randomized Phase III Trial of Initial Salvage Chemotherapy for Patients with Germ-Cell Tumors; NCT02375204). This trial is randomly assigning patients to receive TIP for 4 cycles or TI followed by high-dose CE for 3 cycles.

Novel Approaches in Testicular Cancer

Although most cases of metastatic testicular cancer will be cured, approximately 10% of patients have platinum-refractory disease that remains incurable. Further advances in evaluating the biology of this disease and investigating the mechanism of resistance to treatment are desperately needed. In the era of targeted therapy and immunotherapy, cytotoxic chemotherapy remains the mainstay of treatment for metastatic testicular cancer. Unfortunately, early studies with molecularly targeted therapies such as imatinib, sunitinib (Sutent, Pfizer), thalidomide, and trastuzumab (Herceptin, Genentech) have yielded negative results.[75-78] Studies evaluating the activity of immune checkpoint inhibitors are under way, and results will be reported in the near future.[79] Some investigators are evaluating hypomethylating agents as a means to overcome the mechanism of resistance to platinum chemotherapy in patients with relapsed or refractory germ cell tumors, with early-phase clinical trials ongoing (NCT02429466). Other investigators have evaluated the genomic profile of platinum-refractory germ cell tumors.[80,81] However, consistent targetable genomic alterations have not been identified to date.

Survivorship Issues in Testicular Cancer Survivors

Because the disease of most patients with testicular cancer will be cured, this young population of survivors has been considered a model for evaluating the long-term toxic effects of diagnostic and therapeutic interventions.

Concern is emerging regarding the risk for secondary cancers due to exposure to diagnostic radiation in young patients with testicular cancer undergoing surveillance.

A report on 2569 patients observed for a median of 11 years showed no increased risk for secondary cancer in this group, although follow-up may not have been long enough to detect this risk.[82]

The risk for secondary cancer from surgery, chemotherapy, and radiation therapy has been studied.[83,84] Fung and colleagues evaluated 12,691 patients treated with chemotherapy or surgery and reported a 40% increased risk for solid cancers among patients receiving chemotherapy.[85] In survivors of testicular cancer, cumulative doses of etoposide have been associated with an increased risk for secondary leukemia that typically exhibits a short latency period, a chromosomal translocation (11q23 and 21q22), and rearrangement of the mixed-lineage leukemia gene.[83] The available data on testicular cancer suggest that the risk for secondary leukemia is dose-related, and that the risk of treatment with a total dose of etoposide of more than 2 g is approximately 2% to 3%.[69,86,87]

Testicular cancer survivors are also at risk for multiple other late consequences of therapy, including metabolic syndrome, cardiovascular disease, hypertension, infertility, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, and psychosocial disorders.[88-93] A multi-institutional study evaluating genetic predisposition to long-term cisplatin toxicities, identifying single-nucleotide polymorphisms associated with these toxicities, and collecting data regarding various cardiovascular risk factors in testicular cancer survivors, is currently under way.

Conclusion

The modern history of testicular cancer is that of an oncologic success story. The advances made in the diagnosis, prognostication, treatment, surgical expertise, and long-term survivorship care have resulted from collaborations among investigators across the globe. Collaborations are aimed at discovery of novel therapies for patients who are not cured by current therapeutic options and researching approaches to reduce the late effects of therapy. It is only with maintaining this collaborative spirit that researchers will hopefully achieve the unified goal of curing every patient with testicular cancer in the future.

Disclosures

Dr Adra and Einhorn have no conflict of interests to disclose.

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