Testicular Cancer: A Reflection on 50 Years of Discovery

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Introduction

The advances in the treatment of testicular cancer are among the great achievements in medicine. Cancer researchers from around the globe have asked and answered nearly every fundamental question about the treatment of patients with testicular cancer. The results are astonishing: cure in 95% of all patients; refined surgical techniques that preserve sexual function; minimization of short-term and long-term toxicities of therapy; FDA approval of several agents due entirely or in part from trials in testicular cancer including vinblastine in the 1960’s, bleomycin in 1973, cisplatin in 1978, etoposide in 1983, and ifosfamide in 1988. This article will help the reader understand this journey to a cure, which in many ways mirrors the history of drug development and cancer management during the 20th century. The basic tenets of cancer care were established, reinforced, or challenged during the methodical study of testicular cancer. These tenets include the use of randomized clinical trials to minimize toxicity and maximize outcomes; the rational utilization of combination chemotherapy; and the integration of care involving medical and surgical specialties.

Early Challenges

Before the era of platinum combination chemotherapy, testicular cancer was curable in its earliest stages with surgery and radiation, but nearly uniformly fatal in patients with advanced disease. The lack of convenient and accurate imaging techniques made effective management more challenging. A patient with testicular cancer was evaluated by physical examination, and radiographic procedures which may include chest x-ray, abdominal x-ray, urogram, venacavogram, or lymph angiogram and many patients required surgical staging. The ability to diagnose, stage, assess response, detect relapse, and estimate prognosis took a major leap forward with the discovery of human chorionic gonadotropin (hCG) and α-fetoprotein (AFP) in 1927 and 1956, respectively.1,2 The demonstration of hCG in the urine of patients with testicular cancer, first reported in 1937, significantly improved the accuracy of detecting advanced stage disease.3,4 By the late 1970s and early 1980s, surgical staging was no longer required with the routine use of AFP, hCG, and computed tomography scans.5

In the years following World War II, the successful treatment of testicular cancer included orchiectomy with retroperitoneal lymph node dissection (RPLND), radiation, or both, regardless of histology. Seminomas were more radiation-sensitive.6 Between 1920 and 1965, 414 cases of testicular cancer were reported from Roswell Park.7 For patients with pure seminoma, orchiectomy was followed by RPLND or radiation to pelvic and para-aortic lymph nodes. Either approach resulted in similar survival; therefore, postorchiectomy radiation became standard practice. Before 1949, if embryonal carcinoma was present, higher doses of radiation were given. Given the relative radiation-resistance of embryonal carcinoma, RPLND soon replaced radiation if nonseminomatous germ cell tumors (NSGCT) were present. Each of these observations were confirmed from a series of patients (n = 510) with testicular cancer treated at Walter Reed Army Hospital (Washington, DC) from 1940 to 1964.8 A 95% cure rate was reported in patients with seminoma treated with orchiectomy and radiation therapy. If distant metastases were found, radiation was given to the abdomen, mediastinum, supraclavicular area and even to lung metastases. In their series of 127 patients with NSGCT, no patients with lymph node involvement responded to radiation, and all died within 2 years. RPLND replaced radiation for patients with stage I or II NSGCT, achieving cures in nearly 50% of patients with non-metastatic, lymph node (LN) –positive disease.

Further refinements in the management of patients with stage I seminoma challenged the need for adjuvant radiation, reduced the dose and fields of radiation for those receiving it, and broadened the treatment options to include adjuvant chemotherapy. Today, the treatment options for stage I seminoma following orchiectomy include surveillance, 20 Gy radiation to the ipsilateral RPLN’s, or one to two cycles of carboplatin. Long-term survival is nearly 100%, irrespective of the initial option chosen.9-11 For patients with low volume (<3 cm LN) stage II seminoma, 30 to 36 Gy radiation to the para-aortic and ipsilateral iliac lymph nodes remains standard,12 whereas chemotherapy (regimen of bleomycin, etoposide, and cisplatin [BEP] × 3 or regimen of etoposide and cisplatin [EP] × 4) is preferred for patients with bulkier disease. The management of residual masses greater than 3 cm following chemotherapy has been aided with positron emission tomography imaging. A positive positron emission tomography image (standard uptake value > 4) may represent active seminoma and surgical resection is considered.13

The treatment of stage I and II NSGCT was dependent on performing a RPLND. Full bilateral suprarenal dissections with wide templates removing all lymphatic tissues between the ureters were performed routinely but were associated with significant morbidity.14,15 In the 1970s and 1980s, elegant lymph node mapping studies elucidating the drainage patterns of right versus left-sided tumors were performed in Europe and at Memorial Sloan-Kettering Cancer Center (MSKCC) and Indiana University.15-17 Elimination of the suprarenal component of LNs was possible based on studies by Donohue et al,15
who demonstrated suprarenal LN’s were rarely involved in lower stage tumors and should be removed only in some patients with bulkier disease. Retrograde ejaculation was a common complication for patients undergoing bilateral RPLND. Techniques to preserve the postganglionic sympathetic nerve fibers resulted in preservation of seminal emission and antegrade ejaculation.18-24 This modified unilateral RPLND preserves ejaculation in 90% of patients.

Subsequent research further refined the role of RPLND. Key findings included: residual masses in the RP may contain necrosis, teratoma, or viable germ cell tumor (GCT), the presence of teratoma in the orchietomy is predictive of teratoma in the RPLN, the histology in postchemotherapy (PC)–RPLNs predict the histology of residual masses elsewhere, particularly the lungs, and 95% 2-year progression-free survival is now achieved with a modified, bilateral, PC-RPLND in patients with low volume stage II disease.25-28 One area of management which remains unsettled is the role of PC-RPLND in patients with stage II or III disease achieving a serologic and radiographic complete response (CR). Proponents of observation at Indiana University cite the 15-year cancer-specific survival of 97% reported with this approach,29 while investigators at MSKCC recommend PC-RPLND in most patients, citing the presence of viable GCT and teratoma in some patients with normal-size RPLNs on CT.30

Three treatment options, which include active surveillance, nerve-sparing RPLND or adjuvant chemotherapy, are standard for stage I NSGCT, resulting in 98% to 100% long-term cure rates.31-34 Patients are characterized as high risk (relapse rates 50% with surveillance) versus low risk (15% relapse rates with surveillance) based on the presence of vascular invasion and embryonal predominant histology.11,31 Patients with low volume stage II NSGCT (RPLN < 3 cm) and normal postorchiectomy hCG and AFP are generally managed with RPLND, while those with higher volume stage II disease or rising markers receive chemotherapy (BEP × 3 or EP × 4).36,37 Cures are achieved in approximately 95% of all patients.

Pretcisplatin Chemotherapy Era

Fifty years ago, a diagnosis of metastatic testicular cancer meant a negligible cure rate with 90% mortality within 1 year. During the 1950s and 1960s, the arsenal of chemotherapeutics now included alkylating agents, antimetabolites such as methotrexate, antibiotics including actinomycin-D, and plant products including the vinca alkaloids.38 Actinomycin-D, isolated from cultures of Streptomyces paravollus, was of particular interest in testicular cancer based on the report of responses seen in pediatric patients with Wilms’ tumor, a fetal tumor in the kidney, reported by Farber et al.39

The initial chemosensitivity of testicular cancer was demonstrated at MSKCC in 1960. Li et al.40 reported actinomycin-D based therapy resulted in durable remissions in 10% to 20% of patients and a cure in approximately 5%. Li et al.41 also reported the use of methotrexate to cure a patient with gestational choriocarcinoma, a landmark event in 1956. Li et al.42 studied 36 patients with advanced testicular cancer utilizing actinomycin-D combined with an alkylating agent (chlorambucil) and antimetabolite (methotrexate) in men with advanced testicular cancer. The authors determined the best chance of deriving benefit came with the combination of agents from different classes. The concept of combined drug therapy given in a cyclical manner was not new in medicine, as it had been used effectively to treat tuberculosis, but challenged the dogma of the day in cancer treatment. Li et al. also recognized the significance of monitoring hCG in the urine as a marker of persistent, microscopic disease, even when the radiographs demonstrate a CR.

The plant Vinca rosea Linn (periwinkle) was widely cultivated as an ornamental in gardens throughout the world and enjoyed a popular reputation as a medicinal, including as an effective oral hypoglycemic agent.42 Hertz et al demonstrated the activity of vinblastine in patients with methotrexate-resistant choriocarcinoma.33 The activity of vinblastine in testicular cancer was further characterized by Samuels and Howe at MD Anderson in 1970.44 Based on this and other work demonstrating the activity of bleomycin, Samuels and Howe studied the combination of vinblastine plus bleomycin, each with comparable single-agent activity to actinomycin-D, in the first-line treatment of patients with advanced testicular cancer, resulting in a 32% CR rate in 50 patients, and remission greater than 2 years in half of patients achieving a CR.44-46

Era of Cisplatin

The discovery of cis-diaminodichloroplatinum by Rosenberg et al.47 in 1965 is a landmark event in the history of oncology and the single most important discovery in the treatment of metastatic testicular cancer. Platinum is a component of first-line chemotherapy in over a dozen tumor types today. Rosenberg, a biophysicist at Michigan State University, examined whether electrical currents played a role in cellular division. In order to examine this, Escherichia coli cells growing in ammonium chloride had a current applied to them through platinum electrodes. After additional investigation, it was determined that inhibition of cellular division was not due to the electrical current, but platinum hydrolysis products formed from the platinum electrode.

In 1971, the drug development of cisplatin began following the observation of responses in patients with human malignancies, including testicular cancer, by Hill et al.48 Based on the observations from Hill, Higby et al.49 at Roswell Park conducted a phase I study of cisplatin which included 11 patients with refractory testicular cancer (previously treated with actinomycin-D–based regimens). They reported nine of 11 responded to cisplatin, including complete several CRs, an unprecedented finding for a phase I trial even today.49 The toxicity was substantial; however, as irreversible renal failure was observed in some patients and nausea/vomiting (sometimes lasting weeks) was universal, necessitating hospitalization for all patients.

The addition of cisplatin to the regimen of vinblastine plus bleomycin, known as the PVB regimen, was introduced by Einhorn and Donahue50 at Indiana University in 1974. In this phase II study, patients with advanced testicular cancer received four cycles of PVB. Responding patients were also treated with maintenance vinblastine for an additional 21 months. Patients with persistent nodes in the abdomen underwent RPLND. Thirty three of 47 patients achieved a CR with chemotherapy alone resulting in a then astonishing 5-year survival rate of 64%, a 1 log increase in the cure rate compared with contemporaneous actinomycin-D based chemotherapy in metastatic testicular cancer. Based on these stunning phase II results, the US Food and Drug Administration granted approval for cisplatin as a commercial drug, even in the absence of a randomized trial.

Sequential studies from Indiana University testing PVB were aimed at reducing the neuromuscular and myelosuppressive toxicity of the regimen from vinblastine and challenging the tenet of maintenance therapy. The first phase III study (1976-1978) randomly assigned patients to receive PVB with vinblastine given at 0.4 mg/kg/cycle as a control arm versus 0.3 mg/kg/cycle. No difference was
reported as 73% of patients remained long-term survivors with no evidence of disease (NED). These results were confirmed by a more robust study conducted by the European Organization for Research and Treatment of Cancer (EORTC). The next phase III study (1978-1981) from Indiana University randomly assigned patients to receive PVB with or without doxorubicin with a second random assignment to with or without maintenance vinblastine for an additional 21 months. There was no improvement in survival with the addition of doxorubicin or maintenance therapy. Therefore, PVB × 4 cycles became standard therapy.

The next major advance in the treatment of testicular cancer came with the discovery of etoposide. The dried roots from the American mandrake containing podophyllotoxin were cultivated by native North Americans and natives of Himalaya and used as an emetic agent and to treat worm infections. Etoposide, a synthesized derivative of the podophyllotoxin, entered cancer trials in 1971 and was reported to be active as a single agent in patients with refractory GCT. Based on a leukemia mouse model demonstrating the synergistic effects of etoposide with cisplatin, combination studies were evaluated as second-line therapy in patients not cured with PVB. In a trial from the Southeastern Cancer Study Group (SECSG), 43% of patients achieved a CR, and 23% remained disease-free long term. This was the first time in oncology that a relapsed solid tumor had been cured with second-line chemotherapy.

While work continued at Indiana University refining the PVB regimen, investigators at MSKCC had been refining their own chemotherapy program against testicular cancer, consisting of six successive regimens beginning in 1972. In 1975, cisplatin was added to the regimen referred to as VAB-6, consisting of cisplatin, vinblastine, bleomycin, cyclophosphamide, and actinomycin-D with or without maintenance therapy, and resulting in a CR rate of 67% with chemotherapy alone. Bosl et al at MSKCC conducted a randomized trial comparing VAB-6 with EP. Based on a set of prognostic variables (lactate dehydrogenase, hCG, number of sites of metastatic disease) reported from MSKCC researchers, only patients with good-risk disease were eligible. Responses were seen in greater than 90% with either treatment, however more patients receiving VAB-6 had residual GCT at the time of surgery and patients treated with EP had numerically superior survival with less toxicity. Based on these results, EP became standard treatment.

Investigators at Indiana University and the SECSG also studied etoposide as an alternative to vinblastine, in the first-line setting. A randomized phase III study compared PVB with BEP from 1981 to 1984. Two hundred and forty-four patients were randomly assigned. Seventy-eight percent of patients receiving BEP were cured compared with 66% receiving PVB. Based on this improved efficacy and less toxicity, BEP became our standard of care. Attempts have been made to improve on the efficacy, toxicity, and convenience of the BEP regimen by testing alternative dose and schedules of BEP. The Australian and New Zealand Germ Cell trial group randomly assigned patients to receive BEP per the Indiana regimen (cisplatin 20 mg/m² IV day 1 through 5, etoposide 100 mg/m² IV day 1 through 5 every 3 weeks and bleomycin 30 units intravenously [IV] weekly) versus cisplatin 100 mg/m² day 1, etoposide 120 mg/m² day 1 through 3 and bleomycin 30 units IV weekly. The Indiana regimen resulted in numerically superior survival and remains standard.

Each successive cycle of BEP resulted in cumulative chemotherapy-induced nephrotoxicity, neurotoxicity, otoxicity, and bleomycin-induced pulmonary toxicity. Therefore, from 1984 to 1987, the SECSG randomly assigned patients with good risk disease to receive three versus four cycles of BEP. This was done in an attempt to eliminate the most toxic cycle of therapy, due to cumulative toxicity. One hundred and eighty-four patients were enrolled and 92% cure rates were reported on each arm. Remarkably, 98% of metastatic patients with an hCG of less than 1,000 were cured with only three cycles of BEP. In a larger study, the EORTC randomly assigned patients with good risk disease to either BEP × 3 versus BEP × 3 then EP × 1; they reported a 90% progression-free survival in both arms and no difference in efficacy between a 3- and 5-day regimen of EP, although the 3-day regimen had more hematologic toxicity, otoxicity, and nausea. For patients with good risk metastatic disease, standard therapy remains BEP × 3 or EP × 4. An attempt to define the superioritiy of one regimen over the other was undertaken by the French Federation of Cancer Centers who randomly assigned patients with good risk disease to either of these regimens, reporting 91% and 86% durable responses with BEP × 3 and EP × 4, respectively. Thus from 1974 to 1987 randomized studies substituted etoposide for vinblastine with decreased toxicity and increased efficacy and shortened duration of therapy from 2 years to 9 weeks for most patients with metastatic disease.

Two achievements in the 1990s laid the groundwork for additional success in the management of patients with testicular cancer, namely, identification of universally agreed on prognostic groups and the discovery of the first selective serotonin type 3 (5HT3) receptor antagonists. In 1997, following a multinational analysis, a consensus statement for metastatic GCT was published by the International Germ Cell Cancer Collaborative Group (IGCCCG). The IGCCCG risk stratification system takes into account the primary tumor site, metastatic sites, and amplitude of serum tumor marker levels. Patients with advanced GCT are now subdivided into 3 risk groups: good (> 90% rate of cure), intermediate (75% rate of cure) and poor (50% rate of cure). The second major achievement came in 1991. Before the advent of effective antiemetics, cisplatin-based chemotherapy was extremely difficult for most patients, as frequent and prolonged nausea/vomiting was universal. In one phase III study, the median number of emetic episodes on day 1 of chemotherapy was 10. Before the US Food and Drug Administration approval of ondansetron in 1991, antiemetic prophylaxis for cisplatin consisted of dexamethasone, lorazepam and high-doses of metoclopramide, which frequently resulted in troubling extrapyramidal adverse effects in young patients. Today the median number of emetic episodes on day 1 with modern antiemetic therapy is zero.

Bleomycin causes severe pulmonary toxicity in a dose-related fashion in some patients. Investigators from the EORTC randomly assigned patients to BEP × 4 versus EP × 4, demonstrating inferior results with the deletion of bleomycin (95% vs 87% cure rates). These results confirmed the importance of bleomycin reported from an earlier study from the Australasian Germ Cell Trial Group comparing PVB with PV and another trial from the Eastern Cooperative Oncology Group (ECOG) comparing BEP versus EP (95% vs 86% cure rates). Therefore, bleomycin remains a valuable contributor to the overall efficacy of treatment in good-risk patients and can be safely given to most patients when limiting therapy to three cycles.

Additional attempts to reduce toxicity and preserve efficacy in good risk patients included substitution of carboplatin for cisplatin. Unfortunately, carboplatin substitution (a platinum agent with less
nephrotoxicity and emetogenic potential) for cisplatin also results in inferior outcomes.\textsuperscript{73,74} In one study, Bajorin et al.\textsuperscript{73} randomly assigned patients to receive four cycles of VP versus etoposide plus carboplatin (EC), reporting a 10% inferior relapse free survival with EC. In another study comparing bleomycin plus etoposide with either cisplatin (EC), reporting a 10% inferior relapse free survival with EC. In another study comparing bleomycin plus etoposide with either cisplatin or carboplatin, relapse rates more than doubled with carboplatin (32% v 13%) resulting in more deaths.\textsuperscript{74}

While greater than 90% of patients with good risk metastatic disease are cured with chemotherapy, patients with intermediate- or poor-risk disease face of much less certain future. The worldwide standard for poor-risk disease is four cycles of triple-drug therapy, but poor-risk disease face of much less certain future. The worldwide standard for poor-risk disease is four cycles of triple-drug therapy, but nearly half of these patients are not cured. Therefore, intensification of therapy beyond BEP X 4 has been investigated. The SECSG evaluated BEP comparing double dose (40 mg/m\textsuperscript{2} day 1 through 5) cisplatin versus standard dose (20 mg/m\textsuperscript{2} day 1 through 5) cisplatin for four cycles each in 151 randomly assigned patients.\textsuperscript{75} Two thirds of patients in each arm were cured. The EORTC randomly assigned patients to BEP or without paclitaxel (T) in patients with intermediate risk disease demonstrating no survival difference in 337 randomly assigned patients, although 3-year progression-free survival favored the T-BEP arm (79 v 71%).\textsuperscript{76} Investigators from ECOG randomly assigned 304 men with advanced disseminated GCT to BEP X 4 or cisplatin, ifosfamide, and etoposide (VIP) X 4. Overall complete remission rate and 2-year overall survival (VIP, 74%; BEP, 71%) were not significantly different between the two treatments, despite more toxicity in the VIP arms.\textsuperscript{77} Two randomized clinical trial compared BEP X 4 with BEP X 2 followed by high-dose chemotherapy as first-line treatment in patients with poor-risk GCT\textsuperscript{78,79} and one trial compared BEP X 4 with VIP X 1 followed by high-dose VIP X 3.\textsuperscript{80} All of these studies failed to demonstrate any advantage over BEP X 4 with durable CR’s seen in approximately 50% of patients, and toxicity was more severe with the investigational regimens. Furthermore, some have advocated intensification of therapy based on the rate of tumor marker decline, an independent prognostic variable in patients with poor risk disease, following the first or second cycle of BEP.\textsuperscript{41} This strategy may result in fewer relapses requiring salvage therapy, but has failed to prove a survival advantage to date.

**Salvage Therapy for Relapsed GCT**

Patients who relapse after initial chemotherapy can still be cured with second-line and even third-line regimens. VIP, vinblastine

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### Table 1. Standard Treatment of Seminoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment Options</th>
<th>5-Year OS (%)</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Surveillance or RPLND or BEP × 1</td>
<td>&gt; 99</td>
<td>31, 34</td>
</tr>
<tr>
<td>II</td>
<td>RPLND preferred for nonbulky disease (&lt; 3 cm) BEP × 3 or EP × 4 preferred for bulky disease (&gt; 3 cm)</td>
<td>98</td>
<td>32, 36</td>
</tr>
<tr>
<td>III: Good risk</td>
<td>BEP × 3 or EP × 4</td>
<td>&gt; 90</td>
<td>59, 61, 63, 65</td>
</tr>
<tr>
<td>III: Intermediate/ poor risk</td>
<td>four cycles of 3-drug therapy</td>
<td>50-80</td>
<td>77, 78</td>
</tr>
</tbody>
</table>

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; OS, overall survival; PFS, progression-free survival; RPLND, retroperitoneal lymph-node dissection.

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### Table 2. Standard Treatment of Nonseminomatous Germ Cell Tumors

<table>
<thead>
<tr>
<th>Stage</th>
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<th>5-Year OS (%)</th>
<th>Reference(s)</th>
</tr>
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### Table 3. Landmark Achievements in Testicular Cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Significance</th>
<th>Ref</th>
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<tbody>
<tr>
<td>1937</td>
<td>hCG first reported in the urine of patients with testicular cancer</td>
<td>Improved ability to diagnose, stage, assess response, detect relapse, estimate prognosis</td>
<td>3</td>
</tr>
<tr>
<td>1940s</td>
<td>Seminomas are radiation-sensitive</td>
<td>95% cure rate for stage I or II seminoma prior to era of cisplatin-based chemotherapy</td>
<td>6</td>
</tr>
<tr>
<td>1960</td>
<td>Actinomycin-D based chemotherapy tested in advanced testicular cancer</td>
<td>Durable complete responses and some cures reported for the first time in patients with metastatic testicular cancer</td>
<td>40</td>
</tr>
<tr>
<td>1965</td>
<td>Discovery of cisplatin</td>
<td>Revolutionized the treatment of testicular cancer, achieving cures in &gt; 80% of patients with metastatic disease</td>
<td>47</td>
</tr>
<tr>
<td>1974</td>
<td>PVB regimen first tested 3 versus 4 cycles</td>
<td>Increased cure rate by 1 log compared with contemporaneous chemotherapy</td>
<td>50</td>
</tr>
<tr>
<td>1980s</td>
<td>Nerve-sparing RPLND</td>
<td>Preserves ejaculatory function in &gt; 90% of patients undergoing this procedure</td>
<td>18-24</td>
</tr>
<tr>
<td>1981</td>
<td>PVB with or without maintenance vinblastine</td>
<td>Eliminated need for maintenance therapy</td>
<td>53</td>
</tr>
<tr>
<td>1985</td>
<td>EP regimen</td>
<td>Cures possible in the second-line setting</td>
<td>57</td>
</tr>
<tr>
<td>1987</td>
<td>PVB versus BEP</td>
<td>BEP supplants PVB as standard therapy</td>
<td>61</td>
</tr>
<tr>
<td>1989</td>
<td>BEP × 3 versus 4 cycles in good risk</td>
<td>Eliminates fourth cycle of BEP in good risk patients</td>
<td>63</td>
</tr>
<tr>
<td>1997</td>
<td>IGCCC prognostic groups</td>
<td>Allows for more accurate study of treatment outcomes by risk groups</td>
<td>66</td>
</tr>
<tr>
<td>2007</td>
<td>Largest series to date reported on HDCT in relapsed disease</td>
<td>Cures achieved in &gt; third-line, poor-risk groups, including platinum-refractory patients</td>
<td>89</td>
</tr>
</tbody>
</table>

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; hCG, human chorionic gonadotropin; HDCT, high-dose chemotherapy; IGCCC, International Germ Cell Cancer Collaborative Group; PVB, cisplatin, vinblastine, and bleomycin; RPLND, retroperitoneal lymph-node dissection.
Bone marrow transplantation (BMT) entered patient care in the 1950s and was increasingly successful by the end of the 1960s with the use of platelet transfusion support, improved antibiotics, growth factor support, and more effective cancer drugs. In 1986, investigators at Indiana University began work with high-dose chemotherapy (HDCT) in patients with relapsed testicular cancer. Significant escalation of cisplatin dose is limited by extramedullary toxicities; therefore, high-dose carboplatin and etoposide were evaluated since myelosuppression, which can be managed with bone marrow rescue, is their dose-limiting toxicity. In a phase I/II trial, 33 patients with recurrent disease were treated from 1986 to 1988. Enough bone marrow for two courses of therapy was harvested a few days before chemotherapy. The median time to hematopoietic recovery was about 25 days and 25% achieved a CR. Cures were observed even in the third- and fourth-line setting, which was unprecedented at the time.  

In 1995, it was reported that peripheral blood stem cells (PBSC) resulted in sustained trilineage reconstitution after HDCT more rapidly than bone marrow. Therefore, in 1996, PBSC transplantation could replace BMT for the treatment of recurrent GCT at Indiana University. Einhorn et al reported the experience from Indiana University with HDCT (using carboplatin and etoposide) followed by PBSC rescue in 184 patients with metastatic GCT that had progressed after first-line cisplatin-based chemotherapy. Of the 184 patients, 63% achieved a CR without relapse during a median follow-up of 48 months; 70% of patients who received the treatment as second-line therapy were cured, as were 45% treated in greater than or equal to the third-line setting.

Investigators from MSKCC have also evaluated HDCT, the TI–CE protocol, incorporating paclitaxel and ifosfamide (TTI) as induction chemotherapy and stem cell mobilization, followed by three cycles of high-dose carboplatin and etoposide (HD-CE) and autologous stem-cell transplantation. In their experience, 54 (50%) patients achieved a CR, including 42% with chemotherapy alone and 8% with chemotherapy and surgery. The 5-year disease-free survival was 47% and overall survival was 52%.

Refinements in the use of HDCT continue today. Patients with recurrent disease have been classified into very low, low, intermediate, high, and very high risk categories. In a large 1,500-patient multi-institutional retrospective study, HDCT cured 27% of patients with very high–risk disease compared with only 3% with standard-dose salvage therapy. In addition, two other series report that patients with recurrent disease and unfavorable prognostic features including primary mediastinal NSGCT are curable with HDCT, a result rarely seen with standard-dose therapy. Based on this data, some have argued using HDCT for most patients in the second-line setting, while others have proposed HDCT only in high- or very high–risk groups unlikely to be cured with standard-dose salvage therapy. There are current attempts to address this with a proposed phase III study comparing TIP with TI-CE as initial salvage chemotherapy.

### Long-Term Issues in Survivors

Given the high cure rates in patients with testicular cancer, this young population has been evaluated for the long-term toxicity of diagnostic studies, therapy, and other long-term issues affecting survivors. There has been an emerging concern about the risks of second cancers due to the frequent exposure to diagnostic radiation to the abdomen and pelvis in young patients undergoing active surveillance. van Walraven et al explored this issue in 2,569 men, observed for a median of 11 years, reporting no increased risk of second cancers. However, follow-up may not have been long enough to observe secondary malignancies. Similarly, the risk of treatment-related second cancers from surgery, chemotherapy, and therapeutic radiation has been reported. Fung et al evaluated 12,691 patients treated with chemotherapy or surgery and reported a 40% increased risk for cancers for those receiving chemotherapy. Secondary leukemia is also recognized to result from the cumulative exposure to etoposide, particularly beyond 2000 mg/m². Testicular cancer survivors are also at risk for metabolic syndrome, cardiovascular disease, infertility, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, psychosocial disorders, and behavioral issues including problem drinking. A multi-institutional effort is underway to understand the genetic underpinnings of long-term cisplatin toxicities, identify single nucleotide polymorphisms associated with these toxicities, and to systematically collect data regarding various cardiovascular risk factors in testicular cancer survivors.

### Vexing Issues in Testicular Cancer Remain

The last 50 years of testicular cancer research have produced stunning results, but multiple challenges remain. Ninety-five percent of patients with testicular cancer, including 80% with metastatic disease, can be assured they will be cured. The primary focus today is to develop more effective treatments for those with poor-risk disease, especially those with multiple poor-risk features at diagnosis, and those whose disease has relapsed following first-line chemotherapy. Secondly, patients with late relapse (>2 years from diagnosis) and those with malignant transformation of teratoma are less chemotherapy sensitive. They are managed primarily with surgery and fewer than half will remain continuously free of disease following treatment. Thirdly, common clinical scenarios can still be vexing for clinicians less experienced at managing patients with testicular cancer.

### Final Thoughts

The success in the treatment of testicular cancer is not the result of a single individual or institution, but rather the collective work of an international community of cancer researchers (Tables 1 and 2). Each major discovery is dependent on the discoveries that precede them (Table 3). Refinements in surgical mapping of disease, discovery of radiation and its application to cancer care, isolation of tumor markers initially in the urine and subsequently in the serum, development of preclinical tumor models to test the potential of cancer drugs, development of chemotherapy principles, and the discovery of cisplatin each predated the landmark trial of PVB in 1974. The refinement of chemotherapy at each institution built off the experiences reported from other institutions. This collaborative spirit continues today as an international group of researchers work with a common spirit to ensure no person will die of testicular cancer in the future.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The author(s) indicated no potential conflicts of interest.
AUTHOR CONTRIBUTIONS
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES
17. Weissbach L, Boedefeld EA: Localization of solitary and multiple metastases in stage II nonseminomatous testis tumor as basis for a modified staging lymph node dissection in stage I. J Urol 138:77-82, 1987

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**ASCO Community Research Forum Annual Meeting**

As part of ASCO’s efforts to support community-based researchers, this meeting provides a unique opportunity to discuss barriers and develop solutions to common challenges that are faced in the community research setting, and provides a forum to:

- Collaborate and network with colleagues
- Discuss barriers to conducting research
- Work to develop strategies to effectively conduct community-based research
- Influence the direction of ASCO initiatives
- Provide input on policy issues affecting clinical research

Space is limited, so register early! For more information, visit [asco.org/communityresearchforum](http://asco.org/communityresearchforum).
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