Testicular Cancer: An Oncological Success Story

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Abstract
Testicular cancer has become a model for a curable neoplasm. Our studies with cisplatin combination chemotherapy allow us to conclude that: (a) short-duration intensive induction therapy with the most active agents in optimal dosage is more important than maintenance therapy; (b) modest dose escalation increases toxicity without improving therapeutic efficacy; (c) it is possible to develop curative salvage therapy for refractory germ cell tumors; and (d) preclinical models predicting synergism, such as vinblastine + bleomycin or cisplatin + etoposide have clinical relevance. Finally, testicular cancer has also become a model for new drug development. Cisplatin was approved by the Food and Drug Administration for testis and ovarian cancer, and etoposide and ifosfamide were approved for refractory germ cell tumors. The success of these studies confirms the importance of the continued search for new investigational drugs in all solid tumors.

Introduction
Germ cell tumors are relatively uncommon carcinomas, accounting for only 1% of all male malignancies. The age group affected is a young patient population (ages 15–35), and therefore, the potential for loss of productive years of life has always been significant.

Testis cancer has long been a model for a curable neoplasm (1, 2). Germ cell tumors are uniquely chemosensitive and chemocurable. In addition, surgery alone has a remarkably high cure rate, even in the presence of multiple retroperitoneal lymph nodes (3, 4).

Studies Prior to Cisplatin
Prior to the usage of cisplatin combination chemotherapy, standard chemotherapy for disseminated testicular cancer consisted of dactinomycin, alone or in combination with methotrexate and chlorambucil. Thirty years ago, Li and colleagues (5) at Memorial Sloan Kettering recognized that testis cancer was chemosensitive, with a 50% objective response rate including 10–20% CRs (6) and a 5–10% cure rate. Samuels and colleagues (6) at M. D. Anderson later evaluated vinblastine + bleomycin, a synergistic regimen in preclinical studies, and achieved a 25% long-term disease-free survival. However, the most significant event in curing germ cell tumors was the discovery of cisplatin by Rosenberg et al. (7). Investigators at Roswell Park evaluated cisplatin in previously treated patients with germ cell tumors and obtained three CRs and three partial remissions in 11 patients.

With this background, in August 1974, we began our initial PVB study at Indiana University, using the established two-drug synergistic regimen of vinblastine + bleomycin, and simply adding the then experimental drug cisplatin. The PVB regimen fulfilled our requirements for a successful combination chemotherapy regimen: (a) single-agent activity for each component of the PVB regimen; (b) different and unique mechanism of cytotoxicity for each of the three agents; (c) separate and nonoverlapping toxicity, allowing administration of each drug in full dosage; and (d) evidence of preclinical synergism (vinblastine + bleomycin).

PVB Studies
In 1974, the model for a curable neoplasm was childhood acute leukemia. This model stressed the importance of central nervous system (and testis) sanctuary sites, the importance of effective induction chemotherapy, and the use of long-duration maintenance chemotherapy to achieve “total cell kill.” During this time period, the concept of “aggressive” chemotherapy for a solid tumor, compared, for example, to adult acute leukemia, was only rarely considered.

From 1974 to 1976, we initiated and completed our first PVB study (8). This was our only Phase II study, as all subsequent PVB clinical trials were Phase III studies designed to improve results or mitigate toxicity. The original PVB regimen combined the two older agents, vinblastine (0.2 mg/kg on days 1 and 2 every 3 weeks for four courses) and bleomycin (30 units/week for 12 consecutive weeks) with cisplatin. The dose and schedule mimicked the previous positive Phase II study of single-agent cisplatin in germ cell tumors (9).

As was traditional in the mid-1970s, induction therapy was followed by maintenance chemotherapy (0.3 mg/kg vinblastine monthly for a total of 2 years of chemotherapy). Four courses of PVB induction chemotherapy were used. It was felt that further courses of PVB induction therapy would be of questionable value and would greatly increase the cumulative cisplatin anorexia, nausea, vomiting, ototoxicity, neurotoxicity, and nephrotoxicity, and bleomycin would increase pulmonary fibrosis.

Thirty-three of 47 (70%) patients attained a CR, and an additional 5 patients (11%) were rendered disease-free by post-PVB surgical resection of radiographically persistent disease. This form of combined modality therapy was also investigative and required urological and thoracic surgical expertise (10).


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3 The abbreviations used are: CR, complete remission; PVB, cisplatin + vinblastine + bleomycin; VP-16, etoposide; BEP, bleomycin + etoposide + cisplatin; PVP-16B, cisplatin + VP-16 + bleomycin; NED, no evidence of disease; VIP, VP-16 + ifosfamide + cisplatin; VeiP, vinblastine + ifosfamide + cisplatin.
There were clearly patients who were incurable with chemotherapy or surgery alone who were cured with this combined modality approach. This PVB regimen literally produced a one-log increase in the cure rate compared to contemporary actinomycin-D programs.

In 1976, we completed our PVB Phase II study. We felt it was logical to ask a toxicity question in our subsequent Phase III study, i.e., could we reduce the severe neuromuscular and myelosuppressive toxicity of vinblastine by reducing the dosage from 0.4 to 0.3 mg/kg and still maintain therapeutic efficacy? Fifty-two patients received a control arm of PVB with 0.4 mg/kg vinblastine and an experimental arm with a 25% reduction in the vinblastine dosage. As expected, the lower dose of vinblastine was associated with a significant reduction in toxicity, and the CR and cure rates were similar with the two arms (11). A similar but larger study was conducted by the European Organization for Research and Treatment of Cancer in 214 patients (12). This study also demonstrated similar CR rates (68% with 0.4 mg/kg versus 71% with 0.3 mg/kg vinblastine) and no difference in overall survival. There was a significant increase in neuromuscular and hematological toxicity with the higher vinblastine dosage (P = 0.01).

In 1978, it was standard oncological dogma to use maintenance therapy in chemosensitive disseminated tumors. The major benefit of PVB was always thought to be due to cisplatin combination chemotherapy as induction therapy. Therefore, our third generation PVB study challenged one of the basic tenets of oncology, derived from the childhood leukemia model of total cell kill. Standard induction PVB, with 0.3 mg/kg vinblastine, was given for four courses. Patients achieving a disease-free status were then randomized to a standard arm of 21 months of maintenance vinblastine versus an experimental arm of just 12 weeks of PVB with no further therapy. One hundred thirteen patients entered this study at Indiana University or participating institutions in the Southeastern Cancer Study Group. The relapse rate was only 5%, with or without maintenance vinblastine (13). The Memorial group has also evaluated maintenance therapy (vinblastine plus actinomycin-D) with their VAB VI regimen and also found no benefit for maintenance treatment (14).

**PVB versus BEP**

VP-16 is an epipodophyllotoxin derivative with definite single-agent activity in refractory testicular cancer (15). The combination of cisplatin and etoposide is highly synergistic in preclinical models (16). In 1978, we began our initial salvage chemotherapy studies with cisplatin plus VP-16 in patients who were not cured with PVB or similar induction therapy. VP-16, unlike vinblastine, is essentially devoid of neuromuscular toxicity.

From 1981 through 1984, the Southeastern Cancer Study Group conducted a randomized prospective study comparing PVB and PVP-16B as initial induction chemotherapy (17). No maintenance therapy was given in either arm, and if the markers were normal postchemotherapy but there was persistent radiographic abnormalities, appropriate surgery was done. If carcinoma was found, two more courses of the original induction regimen were given.

A total of 244 patients from 24 institutions entered this trial. Of 121 patients treated with PVB, 74 (61%) had a CR, and another 15 (13%) became disease-free after resection of teratoma (10 patients) or carcinoma (5 patients). Among the 123 patients given PVP-16B, 74 (60%) had a CR, and 28 (23%) became free of disease after resection of teratoma (22 patients) or carcinoma (6 patients). Thus, 74% became disease-free after treatment with PVB and 83% after PVP-16B. Nine patients on PVB and 6 receiving PVP-16B subsequently had recurrences. In the subgroup of advanced disseminated disease, there was a survival advantage for BEP (P = 0.02).

Granulocytopenic toxicity, including granulocytopenic fever, was similar in the two arms. There was a major reduction in neuromuscular toxicity, as manifested by paresthesia, abdominal cramps, ileus, and myalgias. This was significant not only statistically but also clinically. On the basis of this study, which demonstrated a reduction in morbidity and superior survival, we have used BEP since 1984 as first-line therapy for disseminated testicular cancer and have abandoned PVB.

**Subsequent Studies**

**Good-Risk (Minimal-Moderate) Disease.** We have used a staging system that attempts to discriminate good-risk from poor-risk disease (18). In minimal or moderate disease, we began a Phase III study in 1984 evaluating the standard four courses of BEP versus three courses (9 weeks) of BEP. One hundred eighty-four patients entered this study, and 97% achieved a NED status confirming the accuracy of minimal and moderate extent disease as “good-risk.” An identical 92% of patients on each arm are continuously NED (19).

The Eastern Cooperative Oncology Group completed a Phase III study in good-risk disease randomizing patients to a standard arm consisting of BEP for three courses versus the identical therapy but with the deletion of bleomycin (20). One hundred seventy-one patients were evaluable, and 94% attained an NED status with the three-drug regimen compared to 88% for cisplatin + VP-16 (P = 0.20). The failure-free survival favored the bleomycin arm, 86% versus 69% (P = 0.004). Overall survival was also superior for the three-drug regimen, 95% versus 86% (P = 0.011).

Investigators at Memorial Sloan-Kettering Cancer Center and Southwest Oncology Group evaluated four courses of etoposide + either cisplatin or carboplatin (500 mg/m² every 4 weeks). The VP-16 dosage was 100 mg/m² for 5 consecutive days on both arms. Two hundred sixty-five evaluable patients were analyzed. Although the initial NED rate was similar for both arms (90% versus 88%), the relapse rate was 3% versus 12%, and the continuous NED rate was 87% versus 76% favoring the cisplatin arm (P = 0.005; Ref. 21).

**Advanced Disease.** In poor-risk (advanced) disease, we addressed a therapeutic question to test whether double-dose (40 mg/m² × 5) cisplatin could improve the cure rate. One hundred fifty-three patients were evaluable. Unfortunately, there was no evidence of therapeutic superiority for the high-dose cisplatin arm, with 62.2% continuously NED with high dose and 63.6% with standard BEP (22).

A successor study in advanced disease was completed in 1992. The standard arm of BEP was compared to an experimental arm of VIP. The VIP regimen was chosen because of its success as salvage therapy after PVB and/or BEP. This represented a similar philosophy for ifosfamide compared to VP-16, i.e., single-agent activity, incorporation as a curative salvage regimen, and then...
evaluation as first-line therapy. Three hundred four patients entered this intergroup study. With a minimal follow-up of 2 years, 56% are continuously NED with VIP and 57% with BEP (23).

**Salvage Therapy**

Our concept for salvage therapy has always been to use cisplatin plus other active agents not used previously, as long as there was not progression during cisplatin combination chemotherapy. Our initial salvage therapy after BEP had been vinbiastine 0.11 mg/kg days 1 and 2 + ifosfamide 1.2 g/m² × 5 + cisplatin 20 mg/m² × 5 (VeIP) every 3 weeks for four courses. Between 1984 and 1989, 135 patients received this regimen as second-line therapy. Sixty-seven patients (49.6%) achieved NED status, including 15 (11%) NED-teratoma (NED with chemotherapy followed by resection of teratoma) and 10 (7.4%) NED-CA (NED with chemotherapy followed by resection of carcinoma). Thirty-two (23.7%) are continuously NED, compared to 2 of 3 extragonadal seminoma and 0 of 32 nonseminomatous extragonadal patients.

High-dose therapy with carboplatin and VP-16 and autologous bone marrow transplant was first started at Indiana University in 1986. Initially, this was used as a last attempt at curative therapy (third-line or later or following progression during cisplatin therapy). Six of these first 40 patients are 5+ years continuously NED (25). We now use peripheral stem cells and granulocyte-colony-stimulating factor, and we are able to safely administer carboplatin 700 mg/m² × 3 + VP-16 750 mg/m² × 3. We now use this therapy as initial salvage chemotherapy. Twelve of the first 25 patients (48%) are continuously disease-free for 1+ years with this approach (26). However, we continue to use VeIP as initial salvage for seminoma, because 19 of 23 (83%) achieved an NED status and 13 of 23 (56%) are continuously NED (27).

**References**

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