



Antonio Caparello. *Cradle*. Oil on linen, 34" × 54".

Current chemotherapy for patients with metastatic testicular cancer has resulted in high cure rates with acceptable long-term toxicity.

Chemotherapy of Testis Cancer

Pasquale Benedetto, MD

Background: Prior to the use of cisplatin, durable complete remissions of metastatic testis cancer were rare. In 1977, a treatment program including a chemotherapy program of cisplatin, vinblastine, and bleomycin (PVB) led to high response rates and acceptable toxicities in patients with disseminated testis cancer. Since then, the BEP (bleomycin, etoposide, and cisplatin) regimen has been established as standard therapy for good- and poor-risk disease and ifosfamide-based regimens or high-dose chemotherapy with stem cell rescue as salvage therapy.

Methods: The results of those prospective, randomized clinical trials that have markedly improved the outlook of patients with this type of cancer have been reviewed.

Results: Categories of risk have been defined. Standard therapy for both good-risk and poor-risk disease remains BEP therapy. High-dose chemotherapy with autologous bone marrow or peripheral stem cell rescue transplantation is being investigated to overcome chemotherapy resistance.

Conclusions: While the present state of the art for treating metastatic testicular cancer is promising, approximately one third of patients with "poor-risk" disease will not achieve a remission. Trials of new agents and approaches are needed to increase patient survival.

Introduction

Testis cancer is a relatively uncommon malignancy that accounts for an estimated 7,400 new cases in the United States in 1999.¹ Once the leading cause of can-

cer deaths in men between 15 to 34 years of age, it is now estimated that more than 95% of patients with testis cancer will survive the disease with appropriate treatment. The improvement in disease outcome is primarily attributed to the development of effective chemotherapy for advanced disease and serves as a paradigm for the value of the clinical trial.

The modern era of chemotherapy for testis cancer began in the mid 1970s with the identification of the efficacy of cisplatin in the management of the disease. Prior to cisplatin use, durable complete remissions (CRs) of metastatic disease were infrequent, usually less than 15%. In 1977, Einhorn and Donohue² report-

From the Division of Hematology/Oncology at the William J. Harrington Center for Blood Diseases, University of Miami Sylvester Cancer Center, Miami, Fla.

Address reprint requests to Pasquale Benedetto, MD, Division of Hematology/Oncology, William J. Harrington Center for Blood Diseases, 1475 NW 12th Ave (D8-4), Miami, FL 33136.

No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.

Table 1. — Cisplatin, Etoposide, and Bleomycin (BEP) Regimen

Drug	Dose	Administration	
Cisplatin	20 mg/m ² /d	Days 1-5	} q 3 wks
Etoposide	100 mg/m ² /d	Days 1-5	
Bleomycin	30 U/wk	Days 1,8,15	

ed a CR rate of 74% in an initial 50 patients with disseminated testis cancer treated with a combination chemotherapy program composed of cisplatin, vinblastine, and bleomycin (PVB). Overall, 85% of the patients achieved disease-free status with the addition of surgery for the removal of residual masses. Most importantly, the durability of CRs was demonstrated by a relapse rate of less than 10%. At the same time, Cvitkovic and colleagues³ likewise reported a high CR rate with a more complicated regimen of vinblastine, bleomycin, cyclophosphamide, dactinomycin, and cisplatin (VAB III). Given the complexity of the treatment schedule, dosing, and toxicity, as well as the apparent clinical equivalence to the PVB regimen, the VAB programs over time have fallen out of favor.

The toxicities of PVB therapy included azotemia, fever, alopecia, severe myalgia that on occasion required narcotic analgesia, anemia, thrombocytopenia, leukopenia with episodes of nadir sepsis in one third of patients prior to the use of growth factors, and nausea and vomiting in the era prior to 5-HT₃ receptor antagonists. Although substantial, these toxicities were generally reversible. In sequential studies, the CR rate and durability were maintained despite lowering the dose of vinblastine from 0.4 mg/kg per cycle in the original regimen to 0.3 mg/kg per cycle to reduce neuromuscular toxicity.⁴ In addition, maintenance therapy with vinblastine was found to be unnecessary.⁵

While response rates to initial cisplatin-based therapy were high, a substantial number of patients failed to achieve a CR or, although relatively infrequently, relapsed. This established the need for second-line or salvage therapies. Etoposide, an epipodophyllotoxin, emerged as an active drug with a single-agent response rate greater than that of vinblastine^{6,7} and a profile that favored its use in combination therapies due to the lack of neuromuscular toxicity.

In the early 1980s, the Southeastern Cancer Study Group (SECSG) undertook a trial comparing bleomycin, etoposide, and cisplatin (BEP) (Table 1) to "standard" PVB.⁸ The trial included 244 patients who were randomized to treatment with 4 cycles of either PVB or BEP. The results of the trial established therapeutic equivalency of the two regimens in terms of overall response rates (74% in the PVB arm vs 83% in the BEP

arm) with a trend toward improved outcome for patients with advanced disease (high tumor volume) in the BEP arm. More importantly, the toxicity of the BEP regimen was substantially lower in terms of paresthesias, abdominal cramps, and myalgias with similar rates for myelosuppression and pulmonary toxicity, as would be expected. The superior toxicity profile established the BEP regimen as the new standard.

Retrospective analysis of 180 patients with disseminated disease treated on SECSG Protocol 78 GU 240 (PVB trial) revealed that although all patients had metastatic disease, they were not equivalent in the likelihood of achieving CR. Prognostic factors included the number of disease sites, volume of tumor, and/or tumor marker elevation. Based on these parameters, the Indiana University Staging System reclassified extent of disease into "minimal," "moderate," and "advanced" metastatic disease groups (Table 2).⁹ Analyzing the 180 patients treated with a standardized protocol according to these parameters revealed that the likelihood of achieving a CR was 99%, 89%, and 58%, respectively, for the minimal, moderate, and advanced groups. Such analysis led to the designation of "good risk" and "poor risk" groups.

Table 2. — Indiana Classification of Extent of Metastasis for Testicular Cancer

Minimal
1. Elevated HCG and/or AFP only
2. Cervical nodes (± nonpalpable retroperitoneal nodes)
3. Unresectable but nonpalpable retroperitoneal disease
4. Minimal pulmonary metastases — fewer than 5 per lung field and the largest <2 cm (± nonpalpable abdominal disease)
Moderate
5. Palpable abdominal mass as only anatomical disease
6. Moderate pulmonary metastases — 5 to 10 pulmonary metastases per lung field and the largest <3 cm or a mediastinal mass <50% of the intrathoracic diameter or a solitary pulmonary metastasis any size >2 cm (± nonpalpable abdominal disease)
Advanced
7. Advanced pulmonary metastases — mediastinal mass >50% of the intrathoracic diameter or greater than 10 pulmonary metastases per lung field or multiple pulmonary metastases >3 cm (± nonpalpable abdominal disease)
8. Palpable abdominal mass plus pulmonary metastases
8.1 - minimal pulmonary
8.2 - moderate pulmonary
8.3 - advanced pulmonary
9. Hepatic, osseous, or central nervous system metastases
HCG = human chorionic gonadotropin
AFP = α-fetoprotein
From Birch R, Williams S, Cone A, et al. Prognostic factors for favorable outcome in disseminated germ cell tumors. <i>J Clin Oncol.</i> 1986;4:400-407. Reprinted with permission.

The definitions of these prognostic groups have varied among investigators including those at the Memorial Sloan-Kettering Cancer Center (MSKCC), the European Organization of Research and Treatment of Cancer (EORTC), the Medical Research Council (MRC), and the Indiana Group. This resulted in some difficulty comparing therapeutic protocols because of patient selection. To standardize the risk assessment, the International Germ Cell Cancer Collaborative Group (IGCCCG) analyzed the outcomes of 5,202 patients treated on prospective studies in North America, Europe, New Zealand, and Australia. A prognostic model was developed that will serve as a basis for patient selection on future studies (Table 3).¹⁰ Notably, there is no poor-risk group for seminoma patients who overall respond extremely well to cisplatin-based therapy, particularly without prior radiation therapy exposure. Patients with mediastinal nonseminomatous disease by definition are poor risk at presentation.

Good-Risk or Favorable-Outcome Disease

Based on the prognostic groups defined by the Indiana Staging System (Table 2), the SECSG investigated the optimal duration of therapy for patients with minimal or moderate metastatic disease ("good risk") and randomized such patients between two arms that differed only in the number of cycles of BEP.¹¹ Previously, 4 cycles or

12 weeks of therapy had been defined as standard treatment, as indicated above. Given the high potential cure rates in this population, the concept of minimizing toxicity was evaluated. A total of 184 patients were randomized to 3 vs 4 cycles of BEP. Disease-free status was initially achieved in 86 (98%) of 88 patients treated with 3 courses of therapy vs 93 (97%) of 96 patients treated with 4 courses. The relapse rate of five patients in each arm was similar. There was essentially no difference in outcome between the two treatment groups. This study of patients with minimal or moderate metastatic disease as defined by the Indiana Staging System established the adequacy of treatment with 3 cycles of chemotherapy over 9 weeks. Such therapy limits the total exposure to bleomycin to 270 U and the total etoposide dose to 1,500 mg/m², thus reducing the risk of pulmonary fibrosis or hematologic damage, respectively. Overall, 106 (99%) of 107 patients with minimal disease and 73 (95%) of 77 patients with moderate disease achieved disease-free status, thus validating the good prognosis risk assessment of the Indiana Staging System.

In 1998, Saxman et al¹² updated the outcome of the subgroup of 118 patients who were treated at Indiana University. With an actual follow-up of greater than three years for 97.5% of patients, there remains no significant difference between 3 and 4 cycles of BEP for good-risk patients. The authors note that patients with favorable-prognosis disease with initial human chorionic gonadotropin (HCG) levels greater than 1,000 mIU/mL have a poorer outcome compared to those with HCG levels less than 1,000.

Additional strategies for the minimization of tissue damage for the good-risk patient population have attempted to eliminate bleomycin completely from the treatment regimen. Investigators in the Eastern Cooperative Oncology Group (ECOG)¹³ confirmed the importance of bleomycin in good-risk patients treated with 3 cycles of chemotherapy in a trial that randomized patients to either 3 cycles of BEP or to an experimental arm deleting bleomycin (EP). Disease-free status was obtained in 94% of patients in the BEP

Table 3. — International Germ Cell Cancer Collaborative Group (IGCCCG) Risk Classification

	Nonseminoma	Seminoma
Good Risk	Testicular or retroperitoneal primary tumor AFP <1,000 ng/mL HCG <5,000 U/L LDH <1.5 × ULN No nonpulmonary visceral metastases	Any primary site No nonpulmonary visceral metastases Normal AFP Any HCG Any LDH
Intermediate Risk	Testicular or retroperitoneal primary tumor AFP 1,000-10,000 ng/mL HCG 5,000-50,000 U/L LDH 1.5-10 × ULN No nonpulmonary visceral metastases	Any primary site Any nonpulmonary visceral metastases Normal AFP Any HCG Any LDH
Poor Risk	Mediastinal primary tumor Any nonpulmonary visceral metastases AFP >10,000 ng/mL HCG >50,000 U/L LDH >10 × ULN	None

AFP = α-fetoprotein
LDH = lactate dehydrogenase
HCG = human chorionic gonadotropin
ULN = upper limit of normal

From the International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol.* 1997;15:594-603. Reprinted with permission.

arm vs 88% on the EP arm. More treatment failures, including persistent disease at postchemotherapy surgery and relapse from CR, occurred in the EP arm. Also, the overall survival rate was inferior on the EP arm (86%) compared with the BEP arm (95%).

The EORTC trial of 4 cycles of either BE₃₆₀P (European BEP) or E₃₆₀P (without bleomycin) in which the dose per cycle of etoposide was 360 mg/m² also established the inferiority of the non-bleomycin regimen.¹⁴ However, investigators at MSKCC randomized patients to either 4 cycles of etoposide at 500 mg/m² per cycle plus cisplatin (E₅₀₀P) or to VAB-6 (vinblastine, bleomycin, cisplatin, cyclophosphamide, and dactinomycin).¹⁵ Analysis at a median of five years revealed no difference in initial attainment of disease-free status, relapse rate, or late relapses. The E₅₀₀P arm was associated with less emesis, stomatitis, and magnesium wasting, with no pulmonary toxicity, and with higher nadir white blood cell and platelet counts. Of 82 patients on the E₅₀₀P arm, 76 (93%) achieved initial disease-free status similar to the BEP × 3 arm of the SECSG trial, suggesting that 4 courses of this regimen without bleomycin may be equivalent to 3 cycles with bleomycin.

To reduce nephrotoxicity, the Southwest Oncology Group (SWOG) and MSKCC randomized patients to 4 cycles of E₅₀₀ with either cisplatin or carboplatin. Patients treated on the carboplatin arm had an inferior complete response rate, higher relapse rate, and a lower relapse-free survival, all statistically significant.¹⁶ These findings were confirmed in an EORTC trial as well.¹⁷

The data support the use of either 3 cycles of BEP, with an etoposide dose of 500 mg/m² per cycle, or 4 cycles of E₅₀₀P for patients with good-risk metastatic germ cell tumors resulting in equivalent outcomes. However, a reduced dose of etoposide per cycle of 4 cycles as in the European BEP regimens does not allow for the elimination of bleomycin. Carboplatin cannot be substituted for cisplatin in standard-dose therapy. Standard therapy in the United States generally uses 3 cycles of BEP for good-risk patients.

Poor-Risk Disease

The therapeutic triumphs and standardization of treatment for patients with good-risk metastatic testis cancer is not mirrored by the results of studies in the poor-risk population. These patients fall into three categories: nonpulmonary visceral metastases, extragonadal mediastinal primary disease, or exceedingly high tumor markers (β -HCG, α -fetoprotein [AFP], or lactate dehydrogenase). The CR rate for this population ranges between approximately 40% and 60%.^{8,18-20}

In the original BEP vs PVB trial,⁸ there was a trend toward improved outcome for patients with advanced or poor-risk disease, as defined by the Indiana Staging System, treated with BEP. Sixty three percent of such patients were rendered disease-free with BEP vs 38% with PVB ($P=0.06$). In subsequent cooperative group trials, BEP has become the standard therapy for poor-risk patients based on this subset analysis.

To increase the CR rate for patients with poor-risk disease, investigators at the National Cancer Institute (NCI) attempted to escalate the dose of cisplatin to twice the standard dose (DDP). Ozols et al²¹ conducted a trial using DDP (200 mg/m² per cycle). The PVeBV regimen (consisting of DDP, vinblastine, bleomycin, and etoposide) yielded a response rate advantage compared with standard PVB (88% vs 67%, respectively). In addition, the relapse rate of the standard-therapy arm was much higher, 41% vs 17%, respectively. The actuarial five-year survival favored the double-dose cisplatin (78% vs 48%). The Southwest Oncology Group (SWOG) and SECSG performed a direct comparison trial of etoposide plus bleomycin with either standard cisplatin (100 mg/m² per cycle) or high-dose cisplatin (200 mg/m²) in a poor-risk patient population.²² The results revealed no difference between the treatment arms in the percentage of patients alive or continuously disease-free. The advantage of the high-dose cisplatin arm in the NCI trial, which was not substantiated when a similar high-dose regimen was compared to standard BEP, might indicate that the benefit observed in the first trial was at least in part related to the lack of etoposide in the "standard" chemotherapy arm. In the Intergroup trial, the durable response rate of 61% for the BEP arm was similar to the 63% for the double-dose cisplatin arm. This trial yielded results comparable to those of the subset of poor-risk patients treated with BEP on the SECSG PVB vs the BEP trial cited above. Thus, within the confines of manageable toxicity, escalation of the dose of cisplatin does not enhance treatment outcome for poor-risk patients.

Subsequent to the demonstration of the activity of ifosfamide as a single agent^{23,24} and in combination with cisplatin as second-line therapy,²⁵ an Intergroup trial sponsored by the NCI tested the combination of etoposide, ifosfamide, and cisplatin (VIP) compared with BEP as first-line therapy for poor-risk patients. This trial also failed to increase the percentage of durable remissions over the standard BEP arm (56% vs 57%, respectively).²⁰ Likewise, randomized trials comparing BEP to alternating BEP with PVB²⁶ or to BOP/VIP,¹⁸ a program using a dose-intense schedule of bleomycin, vincristine, and cisplatin (BOP) followed by 3 cycles of a modified etoposide, ifosfamide, and cis-

platin (VIP) scheme, did not yield improved results for the experimental arm. An accelerated dose-intensive regimen C-BOP/BEP (cisplatin, carboplatin, vincristine, and infusion bleomycin followed by BEP × 3) piloted by the Royal Marsden Hospital²⁷ suggested an improvement over historical control, but the population of patients was small, the definition of poor-risk was not standardized, and the study was nonrandomized.

Other treatment approaches for the poor-risk patient have included the use of alternating cycles of etoposide plus cisplatin with the VAB-6 regimen. Compared to a similar cohort of patients treated at MSKCC with VAB-6 alone, there was no benefit to the additional drugs and the alternating schema.²⁸ Investigators at the Institut Gustave Roussy²⁹ compared the CISCA(II)/VB(IV) regimen (cyclophosphamide, doxorubicin, cisplatin/vinblastine, and bleomycin) piloted by investigators at M.D. Anderson Cancer Center³⁰ to a concurrent although nonrandomized cohort of patients treated with BEP. Disease-free status was achieved in 9 (53%) of 17 patients with the CISCA program vs 16 (70%) of 23 patients in the BEP group.²⁹ Although a randomized trial was initiated, the results of the single-arm trials would not suggest any significant advantages to the multidrug regimen. The intensive seven-drug POMB/ACE³¹ regimen (cisplatin, vincristine, methotrexate, bleomycin, actinomycin D, cyclophosphamide, and etoposide) has demonstrated a three-year survival of 75% in a subgroup of patients with poor-risk disease as defined by the IGCCCG compared with a historical control value of 50% for a similar cohort of patients. However, the results are limited by the lack of treatment randomization, and further validation is needed.

Despite the various strategies employed above to improve outcome, standard therapy for poor-risk patients outside of a clinical trial remains 4 cycles of BEP. The present ongoing trial in the United States for patients with poor-risk disease compares 4 cycles of conventional-dose BEP to 2 cycles of BEP followed by

tandem courses of high-dose chemotherapy (HDCT) (Fig 1). This study includes patients with intermediate-risk assessment according to the IGCCCG classification. In Europe, patients with intermediate-risk disease are included on a trial of 4 cycles of BEP vs 4 cycles of Taxol/BEP, a new program incorporating Taxol into first-line treatment.

Salvage Therapy

Despite the overall success of chemotherapy, approximately one third of patients with metastatic testicular cancer will not achieve a durable remission with first-line therapy. These failures comprise two groups of patients: those with refractory disease (progression at 4 weeks or less following cisplatin-based chemotherapy) and those who relapse after achieving a first remission.

Subsequent to the success of PVB, clinical trials established single-agent activity for etoposide³² and thereafter for ifosfamide²³ in patients with relapsed or refractory disease. Etoposide was incorporated into first-line therapy in the BEP regimen in the early 1980s and, as above, BEP became the established standard therapy in this country after the results of the SECSG randomized trial demonstrated clinical equivalence of BEP to PVB with a better toxicity profile to the former.

The addition of ifosfamide to cisplatin plus etoposide (VIP) or to vinblastine (VeIP) was evaluated in 1988 in a phase II trial³³ at Indiana University in a population of multiply-relapsed patients who had received at least two prior cisplatin-containing regimens. VIP or VeIP produced a favorable response, ie, CR or disease-free status after surgical resection, in 20 (36%) of 56 patients treated. In the subgroup treated with VIP, 15 (47%) of 32 patients achieved disease-free status. However, only 9 patients remained continuously disease free from 15+ to 42+ months (7 for more than two years). Using the same VIP regimen as second-line therapy, Harstrick et al³⁴ in 1991 reported CRs in 10 of 30 patients — 6 with the addition of surgery. Overall, 5 of the 30 patients remained disease-free. The responses were noted almost exclusively in the subgroup of patients who had achieved CRs to first-line therapy. Therefore, while ifosfamide-based therapy can achieve tumor regression in a cohort of heavily pretreated patients, the overall salvage rate is approximately 16%.

More recent trials have demonstrated single-agent activity for paclitaxel and gemcitabine. Motzer et al³⁵ reported a response rate of 26% (3 CRs, 5 PRs) in 31 patients treated with paclitaxel at a dose of 250 mg/m² as a 24-hour infusion every 3 weeks. Patients in this trial were limited to one prior cisplatin-containing regimen.

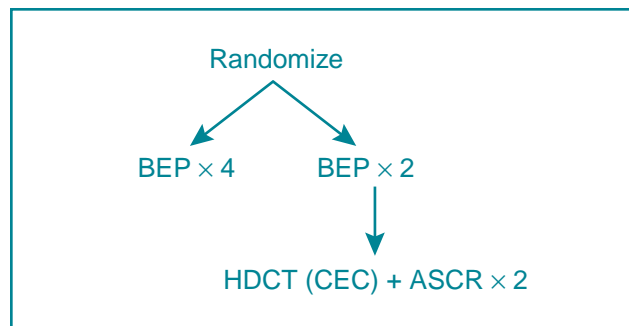


Fig 1. — US Intergroup Trial design for first-line therapy for intermediate and poor-risk patients with germ cell tumors. BEP = bleomycin, etoposide, cisplatin; CEC = carboplatin, etoposide, cyclophosphamide; HDCT = high-dose chemotherapy; ASCR = autologous stem cell rescue.

A trial reported in 1998 demonstrated that the combination of cisplatin and paclitaxel³⁶ achieved an overall response rate of 25% with 1 CR (6%) in 16 patients who had not achieved remission to first-line therapy. The addition of ifosfamide to cisplatin and paclitaxel³⁷ produced a CR rate of 63% in 16 patients with primary testicular neoplasms who had relapsed from initial therapy. Eight patients had no evidence of disease with a median follow-up of 16 months. While intriguing, the follow-up is too short to further comment.

Bokemeyer and colleagues³⁸ treated 31 patients with gemcitabine, and 6 (19%) responded favorably. Although the time to disease progression was short, this population was heavily pretreated: 71% had received HDCT and autologous stem cell rescue (ASCR), and 61% had received prior paclitaxel therapy. In addition, 17 (54%) were considered to be refractory or absolutely refractory to chemotherapy. Three of the responses were seen in patients after HDCT; one of four patients with a mediastinal primary also responded. This level of activity warrants further investigation.

High-dose Chemotherapy With Autologous Bone Marrow or Stem Cell Rescue

Recognizing the exquisite chemosensitivity of germ cell tumors, investigations have led to the use of HDCT with bone marrow or peripheral stem cell rescue as a strategy to overcome chemotherapy resistance to standard drug doses. Germ cell tumors would appear to be an excellent model for dose intensification strategies because the drugs that can be escalated to multiple times the conventional dose range have high single-agent activity in this disease. In addition, the patient population by definition will be young, unlikely to have comorbid medical problems, and therefore capable of tolerating treatment toxicity.

Initial investigations of HDCT with autologous bone marrow transplantation were carried out in populations of patients who were heavily pretreated, the majority of whom were defined as cisplatin-refractory. Of 40 patients treated at Indiana University³⁹ between 1986 and 1989 with 1 or 2 cycles of high-dose carboplatin and etoposide, 12 (30%) achieved a CR. Six patients (15%) had no evidence of disease 24 months after therapy. While only 11% of patients with refractory disease (defined as disease progression within 4 weeks of cisplatin therapy) achieved NED status, the possibility of "cure" in even this small percentage was unexpected with any other therapeutic maneuver. A similar outcome was obtained by Motzer et al.⁴⁰ Of 58 patients, 23 (40%) achieved a CR, five with resection of residual disease. Of these 23 patients, 20 had

received 2 cycles or tandem high-dose therapies. Twelve (21%) remained disease-free at a median follow-up of 28 months. As in the Indiana trial, nearly two thirds of the patients had never achieved a CR to cisplatin-based chemotherapy. Combining the results of several single-institution trials in patients with multiply-relapsed disease treated with HDCT and autologous stem cell support using combinations of carboplatin and etoposide yields an overall durable remission rate of 16%.⁴¹ In the subgroup of patients defined as cisplatin-refractory, 15% achieved durable CRs. These trials support the concept that resistance to cisplatin can be overcome in a small number of patients with massive doses of carboplatin. While the number of cycles of high-dose therapy was variable among the trials, of note in the Indiana trial is that a second cycle of therapy converted 8 of 12 patients from a PR to a CR. The MSKCC trial also suggested that a single HDCT had limited benefit since less than 10% of patients who received 1 cycle of therapy remained continuously disease-free. In these trials, no induction therapy was given.

Subsequent to the demonstration of some limited degree of salvageability of refractory patients with HDCT alone, patients were treated "earlier" in their disease course, ie, in first relapse or when failing to achieve a CR to primary therapy. The results of two trials using conventional salvage chemotherapy, generally ifosfamide-based, followed by one course of HDCT with carboplatin plus etoposide with⁴² or without⁴³ ifosfamide, resulted in approximately one third of patients achieving a durable remission with a median follow-up of 55 and 26 months, respectively. The single-institution trial from Europe reported by Rick et al⁴² included a sample size of more than 150 patients.

The use of tandem HDCT with autologous stem cell rescue after conventional-dose "induction" appears to increase the percentage of long-term disease-free patients. In an Indiana trial,⁴⁴ 15 of 25 patients were rendered disease-free initially, with 52% alive without disease at a median of 26 months (range: 14 to 36 months) posttherapy. In a similar study design at the City of Hope⁴⁵ that included only those patients who were not refractory to cisplatin, 9 (45%) were disease-free at a median of 45 months posttherapy.

Whether the 45% to 52% disease-free survival at a median of greater than 2 years with tandem therapy is really different from the 34% to 39% disease-free survival reported with a single high-dose therapy course remains questionable. Except for the single-institution European trial with 150 patients, the other studies all reported on fewer than 50 patients, and outcomes may have been related to patient selection.

The use of high-dose therapy integrated into the primary treatment of poor-risk patients with germ cell malignancies was reported in 1992 by Droz and colleagues⁴⁶ from the Institut Gustave Roussy. Twenty-eight patients with poor-risk disease with a calculated probability of CR of 0.05 using a prognostic mathematical model based on pretreatment levels of HCG and AFP were treated with a double-dose regimen of cisplatin, vinblastine, cyclophosphamide, and etoposide (modified PVeBV), followed by HDCT with cisplatin, etoposide, cyclophosphamide and ABMT. Seventeen patients achieved a CR, 12 of whom were alive and in continuous CR after a median follow-up of 66 months. These data suggested that the outcome of patients with predicted poor outcome to conventional therapy might be improved with the addition of high-dose therapy.

Similarly, Motzer et al⁴⁷ reported on a phase II trial of high-dose therapy for patients selected for treatment failure to conventional dose therapy on the basis of reduced clearance of tumor markers (prolonged half-life of AFP >7 days, HCG >3 days). Twenty-two of 28 poor-risk patients in the trial received conventional-dose VAB-6 followed by high-dose carboplatin and ABMT. Twelve achieved a CR. The study suggested a trend toward improved survival for the patients treated with HDCT compared to a historical population of poor-risk patients.

Simultaneously, the group at MSKCC treated 13 patients in first relapse or with refractory disease with a similar treatment protocol including HDCT.⁴⁸ Those patients who received the upfront HDCT had less hematologic toxicity. The number of days to granulocyte recovery to 500 was 16 in the upfront group vs 22 in the refractory/relapse group. Likewise, platelet recovery to >50,000 was shortened to 15 days com-

pared with 23, respectively. In addition, there were fewer episodes of culture positive sepsis (12% vs 26%, respectively). The only death occurred in the relapse group. These data suggested that early use of HDCT in a poor-risk population had a better toxicity profile and might result in a better outcome.

While some patients with resistant testis cancer respond to HDCT, the exact algorithm for use of this modality is not definitively established. Two trials that are underway may help to resolve the issue. In Europe, the use of HDCT with ASCR as consolidation therapy to conventional salvage chemotherapy is being evaluated. Patients in first relapse or with incomplete response to initial therapy will receive 2 cycles of "standard" ifosfamide-based therapy with either VIP or VeIP. Those patients with chemosensitive tumor will then be randomized to two additional courses of conventional-dose chemotherapy (arm A) or an additional cycle of conventional-dose therapy followed by a single course of HDCT with carboplatin, etoposide, and cyclophosphamide (Fig 2). In the United States, an Intergroup trial is assessing the value of HDCT as first-line therapy in patients with poor- or intermediate-risk disease. Patients will be randomized upfront to receive 2 cycles of standard BEP followed by tandem HDCT with ASCR or 2 additional cycles of conventional-dose BEP therapy (Fig 1). Since there is a definite salvage of patients with second or subsequent relapse, high-dose therapy would appear at present to be the most optimal salvage therapy for such patients, although the durable remission rate is small.

The various studies of HDCT have defined a number of prognostic factors. Patients with progression of disease entering HDCT fair poorly.⁴⁹ Likewise, patients with primary mediastinal nonseminomatous disease are rarely salvaged with HDCT strategies.^{39,50} Incomplete response to first-line therapy predicts for a poorer outcome. In some trials, the degree of elevation of the serum tumor markers AFP (>1,000 ng/mL) or HCG (>10,000 mIU/mL) as well as the presence of lung metastases were poor prognosis predictors.^{51,52}

Primary Chemotherapy for Stage II Disease

In the era before the advent of effective chemotherapy, the standard of care for patients with stage I or II disease was immediate retroperitoneal lymph node dissection (RPLND). Perhaps the largest series of patients undergoing RPLND has been reported by investigators at Indiana University.⁵³ Between 1965 and 1989, the procedure was performed on 1,180 patients; 174 patients were considered to have clinical

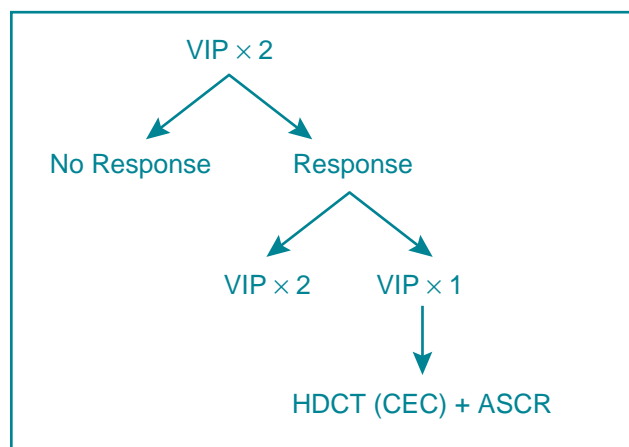


Fig 2. — European trial for patients in first relapse or incomplete response to primary therapy. VIP = etoposide, ifosfamide, cisplatin; HDCT = high-dose chemotherapy; CEC = carboplatin, etoposide, cyclophosphamide; ASCR = autologous stem cell rescue.

stage II disease. However, at surgery, 41 (23%) had no evidence of disease in the lymph nodes examined. Reviewing the data of 140 patients with clinical stage II disease treated between 1979 and 1989 in the cisplatin chemotherapy era, 108 patients had documented retroperitoneal disease. Forty-nine patients received no adjuvant therapy, of which 18 (37%) relapsed and thereafter required chemotherapy. The remaining 59 patients received immediate cisplatin-based chemotherapy. While the overall survival of this patient population was 98%, only 31 patients received monotherapy, ie, surgery alone.

These results may be compared to reports from a number of centers⁵⁴⁻⁵⁶ using primary chemotherapy for stage II disease. The survival in these studies ranged from 96% to 97%, which is comparable to the primary surgery series. The incidence of surgery was 22%, 25%, and 29.5% from the M.D. Anderson Cancer Center, the Mayo Clinic, and the Royal Marsden Hospital, respectively. While 36 of 122 (29.5%) patients in the series by Horwich et al⁵⁶ required postchemotherapy surgery, only 1 specimen contained viable tumor, 29 teratoma. The incidence of surgery postchemotherapy is related to the size of the initial tumor — 39% of patients with stage IIB disease (tumor that was more than 2 cm but less than 5 cm) were taken to surgery, whereas only 17% patients with stage IIA disease (less than 2 cm) had a residual mass. In addition, the presence of teratoma in the primary tumor more likely predicted for teratoma in the retroperitoneum. Thus, in the M.D. Anderson experience, 34% of patients with initial teratoma were ultimately taken to surgery, while only 8% of patients with embryonal cell carcinoma without teratoma in the primary specimen required surgical intervention. Therefore, monotherapy is possible in at least 70% of patients with stage II disease who are initially treated with chemotherapy with an equivalent outcome to primary surgery.

In a report from the Brigham and Women's Hospital and the Dana-Farber Cancer Institute,⁵⁷ all patients with marker-positive disease only who were subjected to primary RPLND ultimately required chemotherapy thereafter.

These reports confirm that the survival for patients with stage II testicular cancer is high and essentially equivalent with either primary chemotherapy or initial surgery. Those patients with marker-positive disease should always be treated with chemotherapy as this subgroup is rarely cured by surgical techniques alone. Patients with pure embryonal cell carcinoma have a low incidence of surgery postchemotherapy and also are likely to require only one modality for successful outcome. Those patients with initial large volume dis-

ease or teratoma in the primary are most likely to undergo surgery but even in these groups the overall incidence of surgery is approximately 34% to 39%. This number represents an upper limit since continued study has suggested that not all patients with residual masses must be subjected to surgery. The size of the residual mass as a percentage of the original size is predictive of the presence of residual viable tumor. As such, some patients without complete radiological response may be followed since the likelihood of teratoma or viable tumor is low.⁵⁸

The approach at our institute favors primary chemotherapy for stage II metastatic disease. Since all of those patients considered appropriate for surgical intervention will by definition have good-risk disease, treatment consists of 3 cycles of BEP.

Primary Chemotherapy for Stage I Nonseminomatous Disease

Therapy after orchiectomy for clinical stage I patients (those with normal markers and negative tomographic studies) classically has been retroperitoneal node dissection. Numerous reports of surveillance programs^{59,62} have established the risk of relapse in stage I patients of approximately 30%. Thus a policy of immediate surgery is of no value for the 70% who will never have metastatic disease. The nearly universal salvage of patients who relapse on surveillance⁶³ has resulted in a shift in this country to the option of surveillance for stage I disease. However, to maintain excellent outcome, surveillance requires meticulous follow-up and should not be advocated in situations where compliance is questionable.

Studies of patients who relapse on surveillance identify factors that increase the risk of relapse: the presence of lymphatic or vascular invasion, the lack of yolk sac elements, the presence of embryonal cell carcinoma, the stage of the primary tumor, or the elevation of markers prior to orchiectomy.⁶³⁻⁶⁶ In the review by Freedman et al⁶⁵ of 259 surveillance patients, the presence of any three of the first four factors resulted in a risk of relapse of 58%. Two factors were associated with a risk of relapse of 24%, and one factor was associated with a risk of relapse of 10%. Vascular invasion of any type was associated with a risk of relapse of 45%.

Using the four criteria above to identify high-risk patients, the Medical Research Council of the United Kingdom treated patients with any three of the four factors with 2 cycles of adjuvant chemotherapy with BE₃₆₀P.⁶⁷ Only 2 of 114 patients developed recurrent disease at a median follow-up of four years, one of whom

did not have a germ cell tumor on review of the primary pathology. Ninety three (82%) have been followed for more than two years. Similarly, Bohlen and colleagues⁶⁸ reported on the outcome of 58 high-risk clinical stage I patients treated with adjuvant chemotherapy consisting of 2 cycles of PVB or BEP. All patients have been followed for more than 32 months. Of the 58 patients, 56 have survived without relapse, 1 relapsed with teratoma only at 22 months, and 1 patient represents a case of late relapse 7.5 years after chemotherapy. A short course of adjuvant chemotherapy appears to be highly effective in reducing the risk of recurrence in a high-risk population.

While the short-term toxicities are manageable, the long-term risks are unclear. The effects on fertility, risk of hypertension, and lung toxicity need to be assessed. Primary chemotherapy for clinical stage I disease may be considered in patients who are at high risk for failure on surveillance and who are judged to be either poorly compliant with follow-up or psychologically incapable of handling a no-treatment strategy.

Long-term Treatment Toxicity

The high cure rate achievable for the majority of patients with testicular cancer treated with chemotherapy has led to a large number of patients who have survived years after therapy, allowing for the assessment of long-term treatment complications or toxicity. These predominantly fall into five categories: neurologic, pulmonary, vascular, reproductive, and hematologic.

Boyer et al⁶⁹ reported an incidence of high-frequency hearing loss in 77% of patients tested at least four years after therapy; 50% had evidence of peripheral nerve damage by electrophysiologic testing. Symptomatic findings were uncommon. Decreased single breath diffusing capacity for carbon monoxide was noted in 20%, all of whom were smokers. No apparent increased risk of ischemic heart disease was noted. Stoter et al⁷⁰ reported an incidence of hypertension in 16%, Raynaud's phenomenon in 23%, and ototoxicity in 25%. These results were derived from a questionnaire and retrospective review of patient charts and are a reasonable estimate of symptomatic toxicity.

While reduced spermatogenesis has been reported by various investigators even prior to the initiation of chemotherapy, recovery occurs in at least half of the patients. In a study of 54 patients treated with chemotherapy and surgery, 72% were either azoospermic or oligospermic prior to therapy. Interestingly, only 48% had azoospermia or oligospermia after therapy; however, the percentage of patients who were

azoospermic had increased to 28% from a pretreatment incidence of 4%.⁷¹ With modern fertility techniques, it is estimated that that nearly three quarters of the survivors could potentially father children. The incidence of congenital malformations is not apparently increased.

Recent reports⁷² suggest a risk of leukemogenesis associated with etoposide therapy. These data derive primarily from the HDCT treatment groups with a cumulative drug dose of greater than 2 g/m². This increased risk affects only 1.3% of all patients who receive drug dose in this range. The risk of leukemia with conventional doses of etoposide chemotherapy is 0.4% to 0.6%, which is small compared to the curative potential of the treatment.⁷³ Secondary solid tumors are not associated with treatment with chemotherapy alone, but they appear to be attributed to exposure to radiation therapy.⁷⁴

Overall, the long-term toxicities associated with curative therapy for testicular cancer are modest and manageable, and most patients are able to return to normal functional status.⁷⁵

Conclusions

With the present state of the art, a high percentage of patients with metastatic testicular cancer can be cured with acceptable long-term toxicity. Those patients with good-risk parameters require only 9 weeks of multiagent (BEP) chemotherapy to achieve disease-free status in greater than 90% of cases. At present, the best treatment for patients with poor-risk disease remains 12 weeks of BEP. However, with this therapy, at least one third of patients will not achieve a remission. Studies of newer agents in combination with standard drug therapy and/or the integration of high-dose therapy into first-line treatment represent present strategies to increase the survival of patients in this subgroup.

Salvage therapy with conventional-dose ifosfamide-based chemotherapy or HDCT without induction therapy yields durable remissions in a minority of patients. Ongoing studies may help to identify those patients who will benefit by intensive-dose strategies. Newer agents such as gemcitabine and paclitaxel hold promise of future treatment success.

References

1. Landis SH, Murray T, Bolden S, et al. Cancer statistics, 1999. *CA Cancer J Clin.* 1999;49:8-31.
2. Einhorn LH, Donohue J. Cis-Diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated

testicular cancer. *Ann Intern Med.* 1977;87:293-298.

3. Cvitkovic E, Hayes D, Golbey R. Primary combination chemotherapy (VAB III) for metastatic or unresectable germ cell tumors. *Proc Annu Meet Am Soc Clin Oncol.* 1976;17:296. Abstract.

4. Einhorn LH, Williams SD. Chemotherapy of disseminated testicular cancer: a random prospective study. *Cancer.* 1980;46:1339-1344.

5. Einhorn LH, Williams SD, Troner M, et al. The role of maintenance therapy in disseminated testicular cancer. *N Engl J Med.* 1981;305:727-731.

6. Williams SD, Einhorn LH, Greco FA, et al. VP-16-213 salvage therapy for refractory germinal neoplasms. *Cancer.* 1980;46:2154-2158.

7. Mortimer J, Bukowski RM, Montie J, et al. VP16-213, cisplatin, and adriamycin salvage therapy of refractory and/or recurrent non-seminomatous germ cell neoplasms. *Cancer Chemother Pharmacol.* 1982;7:215-218.

8. Williams SD, Birch R, Einhorn LH, et al. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. *N Engl J Med.* 1987;316:1435-1440.

9. Birch R, Williams S, Cone A, et al. Prognostic factors for favorable outcome in disseminated germ cell tumors. *J Clin Oncol.* 1986;4:400-407.

10. Schmoll HJ, Beyer J. Prognostic factors in metastatic germ cell tumors. *Semin Oncol.* 1998;25:174-185.

11. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. *J Clin Oncol.* 1989;7:387-391.

12. Saxman SB, Finch D, Gonin R, et al. Long term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: the Indiana University experience. *J Clin Oncol.* 1998;16:702-706.

13. Loehrer PJ Sr, Johnson D, Elson P, et al. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. *J Clin Oncol.* 1995;13:470-476.

14. De Wit R, Stoter G, Kaye SB, et al. Importance of bleomycin in combination chemotherapy for good-prognosis testicular non-seminoma: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group. *J Clin Oncol.* 1997;15:1837-1843.

15. Bosl GJ, Geller NL, Bajorin D, et al. A randomized trial of etoposide + cisplatin versus vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin in patients with good-prognosis germ cell tumors. *J Clin Oncol.* 1988;6:1231-1238.

16. Bajorin DF, Sarosdy MF, Pfister DG, 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.

17. Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol.* 1997;15:1844-1852.

18. Kaye SB, Mead GM, Fossa S, et al. An MRC/EORTC randomized trial in poor prognosis metastatic teratoma, comparing BEP with BOP/VIP. *Proc Annu Meet Am Soc Clin Oncol.* 1995;14:246. Abstract.

19. Droz JP, Pico JL, Turns M, et al. No evidence of a benefit of early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor-risk non-seminomatous germ cell tumors: preliminary results of a randomized trial. *Proc Annu Meet Am Soc Clin Oncol.* 1995;14:239. Abstract.

20. Nichols CR, Loehrer PJ, Einhorn LH, et al. Phase III study of cisplatin, etoposide, and bleomycin or etoposide, ifosfamide, and cisplatin in advanced germ cell tumors: an Intergroup trial. *Proc Annu Meet Am Soc Clin Oncol.* 1995;14:239. Abstract.

21. Ozols RF, Ihde DC, Linehan WM, et al. A randomized trial of standard chemotherapy vs a high-dose chemotherapy regimen in the treatment of poor prognosis nonseminomatous germ-cell tumors. *J Clin Oncol.* 1988;6:1031-1040.

22. Nichols CR, Williams SD, Loehrer PJ, et al. Randomized study of cisplatin dose intensity in poor-risk germ cell tumors: a South-

eastern Cancer Study Group and Southwest Oncology Group protocol. *J Clin Oncol.* 1991;9:1163-1172.

23. Wheeler BM, Loehrer PJ, Williams SD, et al. Ifosfamide in refractory male germ cell tumors. *J Clin Oncol.* 1986;4:28-34.

24. Scheulen ME, Niederle N, Bremer K, et al. Efficacy of ifosfamide in refractory malignant diseases and uroprotection by mesna: results of a clinical phase II study with 151 patients. *Cancer Treat Rev.* 1983;10(suppl A):93-101.

25. Loehrer PJ Sr, Einhorn LH, Williams SD. VP-16 plus ifosfamide plus cisplatin as salvage therapy in refractory germ cell cancer. *J Clin Oncol.* 1986;4:528-536.

26. de Wit R, Stoter G, Sleijfer DT, et al. Four cycles of BEP versus an alternating regimen of PVB and BEP in patients with poor-prognosis metastatic testicular non-seminoma: a randomised study of the EORTC Genitourinary Tract Cancer Cooperative Group. *Br J Cancer.* 1995;71:1311-1314.

27. Horwich A, Dearnaley DP, Norman A, et al. Accelerated chemotherapy for poor prognosis germ cell tumours. *Eur J Cancer.* 1994;30A:1607-1611.

28. Bosl GJ, Geller NL, Vogelzang NL, et al. Alternating cycles of etoposide plus cisplatin and VAB-6 in the treatment of poor-risk patients with germ cell tumors. *J Clin Oncol.* 1987;5:436-440.

29. Culine S, Theodore C, Bekradda M, et al. Experience with bleomycin, etoposide, cisplatin (BEP) and alternating cisplatin, cyclophosphamide, doxorubicin (CISCA(II)), vinblastine, bleomycin (VB(IV)) regimens of chemotherapy in poor-risk nonseminomatous germ cell tumors. *Am J Clin Oncol.* 1997;20:184-188.

30. Samuels ML, Lanzotti VJ, Holoye PY, et al. Combination chemotherapy in germinal cell tumors. *Cancer Treat Rev.* 1976;3:185-204.

31. Bower M, Newlands ES, Holden L, et al. Treatment of men with metastatic non-seminomatous germ cell tumours with cyclical POMB/ACE chemotherapy. *Ann Oncol.* 1997;8:477-483

32. Williams SD, Einhorn LH. Etoposide salvage therapy for refractory germ cell tumors: an update. *Cancer Treat Rev.* 1982;9(suppl A):67-71.

33. Loehrer PJ Sr, Lauer R, Roth BJ, et al. Salvage therapy in recurrent germ cell cancer: ifosfamide and cisplatin plus either vinblastine or etoposide. *Ann Intern Med.* 1988;109:540-546.

34. Harstrick A, Schmoll HJ, Wilke H, et al. Cisplatin, etoposide, and ifosfamide salvage therapy for refractory or relapsing germ cell carcinoma. *J Clin Oncol.* 1991;9:1549-1555.

35. Motzer RJ, Bajorin DF, Schwartz LH, et al. Phase II trial of paclitaxel shows antitumor activity in patients with previously treated germ cell tumors. *J Clin Oncol.* 1994;12:2277-2283.

36. Tjulandin SA, Titov DA, Breder VV, et al. Paclitaxel and cisplatin as salvage treatment in patients with non-seminomatous germ cell tumour who failed to achieve a complete remission on induction chemotherapy. *Clin Oncol (R Coll Radiol).* 1998;10:297-300.

37. Motzer RJ. Paclitaxel in salvage therapy for germ cell tumors. *Semin Oncol.* 1997;24(5 suppl 15):S15-S85.

38. Bokemeyer C, Gerl A, Schoffski P, et al. Gemcitabine in patients with relapsed or cisplatin-refractory testicular cancer. *J Clin Oncol.* 1999;17:512-516.

39. Broun ER, Nichols CR, Kneebone P, et al. Long-term outcome of patients with relapsed and refractory germ cell tumors treated with high-dose chemotherapy and autologous bone marrow rescue. *Ann Intern Med.* 1992;117:124-128.

40. Motzer RJ, Mazumdar M, Bosl GJ, et al. High-dose carboplatin, etoposide, and cyclophosphamide for patients with refractory germ cell tumors: treatment results and prognostic factors for survival and toxicity. *J Clin Oncol.* 1996;14:1098-1105.

41. Sobel RM, Vogelzang NJ. High-dose chemotherapy with autologous stem-cell support for germ cell tumors: a critical review. *Semin Oncol.* 1999;26:106-118.

42. Rick O, Beyer J, Kingreen D, et al. High-dose chemotherapy in germ cell tumours: a large single centre experience. *Eur J Cancer.* 1998;34:1883-1888.

43. Broun ER, Nichols CR, Turns M, et al. Early salvage therapy for germ cell cancer using high dose chemotherapy with autologous bone marrow support. *Cancer.* 1994;73:1716-1720.

44. Broun ER, Nichols CR, Gize G, et al. Tandem high dose chemotherapy with autologous bone marrow transplantation for initial relapse of testicular germ cell cancer. *Cancer.* 1997;79:1605-1610.

45. Margolin BK, Doroshow JH, Ahn C, et al. Treatment of germ cell cancer with two cycles of high-dose ifosfamide, carboplatin, and etoposide with autologous stem-cell support. *J Clin Oncol*. 1996;14:2631-2637.
46. Droz JP, Pico JL, Ghosn M, et al. A phase II trial of early intensive chemotherapy with autologous bone marrow transplantation in the treatment of poor prognosis non-seminomatous germ cell tumors. *Bull Cancer*. 1992;79:497-507.
47. Motzer RJ, Mazumdar M, Gulati SC, et al. Phase II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. *J Natl Cancer Inst*. 1993;85:1828-1835.
48. Motzer RJ, Gulati SC, Crown JP, et al. High-dose chemotherapy and autologous bone marrow rescue for patients with refractory germ cell tumors: early intervention is better tolerated. *Cancer*. 1992;69:550-556.
49. Beyer J, Kingreen D, Krause M, et al. Long-term survival of patients with recurrent or refractory germ cell tumors after high dose chemotherapy. *Cancer*. 1997;79:161-168.
50. Lotz JP, Andre T, Donsimoni R, et al. High dose chemotherapy with ifosfamide, carboplatin, and etoposide combined with autologous bone marrow transplantation for the treatment of poor-prognosis germ cell tumors and metastatic trophoblastic disease in adults. *Cancer*. 1995;75:874-885.
51. Beyer J, Kramar A, Mandanas R, et al. High-dose chemotherapy as salvage treatment in germ cell tumors: a multivariate analysis of prognostic variables. *J Clin Oncol*. 1996;14:2638-2645.
52. Pico JL, Fadel E, Ibrahim A, et al. High-dose chemotherapy followed by hematological support: experience in the treatment of germ cell tumors. *Bull Cancer*. 1995;82(suppl 1):56S-60S.
53. Donohue JP, Thornhill JA, Foster RS, et al. The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). *J Urol*. 1995;153:85-89.
54. Logothetis CJ, Swanson D, Dexeus F, et al. Primary chemotherapy for clinical stage II nonseminomatous germ cell tumors of the testis: a follow-up of 50 patients. *J Clin Oncol*. 1987;5:906-911.
55. Lerner SE, Mann BS, Blute ML, et al. Primary chemotherapy for clinical stage II nonseminomatous germ cell testicular tumors: selection criteria and long-term results. *Mayo Clin Proc*. 1995;70:821-828.
56. Horwich A, Cullen MH, Stenning SP. Primary chemotherapy after orchidectomy for stage I and II nonseminoma. *Semin Oncol*. 1998;25:154-159.
57. Socinski MA, Garnick MB, Fung CY, et al. What constitutes optimum treatment of low volume nonseminomatous germ cell tumors of the testis (NSGCT): an analysis of 48 patients. *Proc Annu Meet Am Soc Clin Oncol*. 1987;6:105. Abstract.
58. Sheinfeld J, Bajorin D. Management of the postchemotherapy residual mass. *Urol Clin North Am*. 1993;20:133-143.
59. Hoskin P, Dilly S, Easton D, et al. Prognostic factors in stage I non-seminomatous germ cell testicular tumors managed by orchidectomy and surveillance: implications for adjuvant chemotherapy. *J Clin Oncol*. 1986;4:1031-1036.
60. Swanson DA, Johnson DE. M.D. Anderson experience with surveillance for clinical stage I disease. In: Johnson DE, Logothetis CJ, von Eschenbach AC, eds. *Systemic Therapy for Genitourinary Cancers*. Chicago, Ill: Year Book Medical Publishers; 1989:304-311.
61. Sogani PC. Evolution of the management of stage I nonseminomatous germ-cell tumors of the testis. *Urol Clin North Am*. 1991;18:561-573.
62. Pizzocaro G, Zanoni F, Salvioni R, et al. Difficulties of a surveillance study omitting retroperitoneal lymphadenectomy in clinical stage I nonseminomatous germ cell tumors of the testis. *J Urol*. 1987;138:1393-1396.
63. Sternberg CN. Role of primary chemotherapy in stage I and low-volume stage II nonseminomatous germ-cell testis tumors. *Urol Clin North Am*. 1993;20:93-109.
64. Read G, Stenning SP, Cullen MH, et al. Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. *J Clin Oncol*. 1992;10:1762-1768.
65. Freedman LS, Parkinson MC, Jones WG, et al. Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. *Lancet*. 1987;2:294-298.
66. Fung CY, Kalish LA, Brodsky GL, et al. Stage I nonseminomatous germ cell testicular tumor: prediction of metastatic potential by primary histopathology. *J Clin Oncol*. 1988;6:1467-1473.
67. Cullen MH, Stenning SP, Parkinson MC, et al. Short-course adjuvant chemotherapy in high-risk stage I nonseminomatous germ cell tumors of the testis: a Medical Research Council report. *J Clin Oncol*. 1996;14:1106-1113.
68. Bohlen D, Borner M, Sonntag RW, et al. Long-term results following adjuvant chemotherapy in patients with clinical stage I testicular nonseminomatous malignant germ cell tumors with high risk factors. *J Urol*. 1999;161:1148-1152.
69. Boyer M, Raghavan D, Harris PJ, et al. Lack of late toxicity in patients treated with cisplatin-containing combination chemotherapy for metastatic testicular cancer. *J Clin Oncol*. 1990;8:21-26.
70. Stoter G, Koopman A, Vendrik CP, et al. Ten-year survival and late sequelae in testicular cancer patients treated with cisplatin, vinblastine, and bleomycin. *J Clin Oncol*. 1989;7:1099-1104.
71. Nijman JM, Schraffordt Kooops H, Kremer J, et al. Gonadal function after surgery and chemotherapy in men with stage II and III nonseminomatous testicular tumors. *J Clin Oncol*. 1987;5:651-656.
72. Kollmannsberger C, Beyer J, Droz JP, et al. Secondary leukemia following high cumulative doses of etoposide in patients treated for advanced germ cell tumors. *J Clin Oncol*. 1998;16:3386-3391.
73. Nichols CR, Breeden E, Loehrer P, et al. Secondary leukemia associated with a conventional dose of etoposide: review of serial germ cell tumor protocols. *J Natl Cancer Inst*. 1993;85:36-40.
74. Jakob A, Kollmannsberger C, Kanz L, et al. Late toxicity after chemotherapy of malignant testicular tumors [in German]. *Urologe A*. 1998;37:635-647.
75. Roth BJ, Greist A, Kubilis PS, et al. Cisplatin-based combination chemotherapy for disseminated germ cell tumors: long-term follow-up. *J Clin Oncol*. 1988;6:1239-1247.