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Review

Commentary: Combination Chemotherapy of Nonseminomatous Testicular Cancer

S. K. Carter[1] and F. M. Torti[2]

Northern California Cancer Program,
1801 Page Mill Road, Palo Alto, CA 94304, USA

From the onset of the modern era of chemotherapy, testicular carcinoma has been shown to be a responsive tumor. In various reviews of single-agent activity in solid tumors no drug with adequate testing has been demonstrated to be inactive [10, 17]. Testicular tumors were the first solid tumor area in which data indicating the superiority of combination chemotherapy over single agents were recorded. This derived initially from the work of Li et al. [8, 9], who described their results with the three-drug combination of actinomycin D, chlorambucil, and methotrexate. This regimen was able to achieve complete remissions in between 10% and 15% of patients treated, some of these achieving long-term disease-free survival. For a long time these results plateaud as a variety of other combination regimens were evaluated.

The modern era of cancer chemotherapy in testicular cancer revolves around the combination of vinblastine and bleomycin. The combination of vinblastine plus bleomycin was first studied at MD Anderson Hospital, and workers there have the most extensive experience reported with these two drugs alone (Table 1).

Samuels et al. [12] first combined bleomycin with vinblastine for the therapy of testicular tumors, as follows: bleomycin 15 mg IM was administered twice weekly for 5 weeks and vinblastine was given at 0.4–0.6 mg/kg IV in two fractions (days 1 and 2). Fifty patients were treated according to this induction scheme, and if a response was seen additional therapy consisting of three or four courses of the same vinblastine dose and 50% of the dose of bleomycin was given. Sixteen patients achieved complete remission (CR) (32%) with this regimen, and 15 were free of disease after 2 years. Twenty-two other patients experienced partial remission (PR; > 50% reduction in maximum tumor diameter), with a median survival of 32 weeks. Five patients developed interstitial pneumonitis secondary to bleomycin therapy.

Samuels [11] has modified his approach to a regimen in which vinblastine is given at 0.4 mg/kg in two fractions (days 1 and 2) and bleomycin (30 mg in 1,000 cm^3 5% D/W over 24 h) is started on day 2 for 5 additional days. Courses are repeated every 21–28 days for three or four courses. Forty Stage III germinal tumors and four extragonadonal primary tumors have been studied. In 39 evaluable patients with high tumor volume presentations there were 19 with CR (47%) and 10 with PR. In the extragonadal group one CR and one PR were seen. The mean survival of complete responders is 34 weeks with none dead. Toxicity included severe leukopenia in 40, thrombocytopenia in 21, hemolytic anemia in 13, stomatitis in all cases, and bleomycin pneumonitis in 2. It appears that the CR rate is superior to that obtained with intermittent bleomycin-vinblastine.

Samuels has compared his experience with Velban plus biweekly bleomycin in 26 patients with that recorded in 34 who received Velban plus continuous bleomycin. In the biweekly bleomycin group 7 (20%) achieved CR, as against 21 (61%) with the continuous infusion approach. The median survival is also superior in the latter group (78+ weeks as against 48 weeks). These data, Samuels feels, show the clear-cut advantage for the infusion approach with bleomycin.

At the Memorial Sloan-Kettering Cancer Center a series of regimens evolved from the nucleus of vinblastine and bleomycin (Table 2) [6].

The first regimen (VAB I) involved daily doses of a three-drug combination of bleomycin (0.4 mg/kg), actinomycin D (0.0075–0.015 mg/kg), and vinblastine (0.025–0.05 mg/kg) [13]. Each drug was given IV on days 1, 2, and 3, and repeated for two or three doses in 7–14 days as toxicity permitted. Twenty-one patients were treated and 16 were evaluable; of these, eight showed objective responses lasting 1–5 months. Hematologic toxicity was predictable and mucocutaneous toxicity be-

1 Consulting Professor of Medicine, Stanford University, and Clinical Professor of Medicine, University of California, San Francisco
2 Assistant Professor of Medicine Stanford University
Reprint requests should be addressed to: S. K. Carter

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Table 1. Vinblastine plus bleomycin at MD Anderson for treatment of testicular cancer

Regimen	Doses mg/m²		No. of evaluable points	% CR	% CR + PR
	Vinblastine	Bleomycin			
VB-1 [11, 12]	0.2–0.3 mg/kg day 1 and 2	30 units twice weekly IM	51	33	70
VB-2 [11, 12]	0.2–0.3 mg/kg day 5 and 6	30 units/day × 5, continuous IV infusion	3	33	100
VB-3 [11, 12]	0.2–0.3 mg/kg day 1 and 2	30 units/day × 5, continuous IV infusion	61	47	82
SWOG VB-1 modification [15]	0.2 mg/kg day 1 and 2	15 units/m² twice weekly IV	11	45	82
SWOG Controlled study modification of VB-1 [14]	15 mg/m² day 1 and 2	15 units/m² twice weekly IV	48	44	65

Table 2. The VAB regimens of Memorial Hospital for testicular cancer [6]

Regimen	Vinblastine	Bleomycin	Actinomycin D	Other drugs	No. evaluable points	% CR	% of those orig. entered with NED
VAB	0.025–0.05	0.40 units/kg	0.0075–0.015 mg/kg		71	14	12
	All drugs given day 1, 2, 3, 9, 10, 11 Then weekly maintenance: VLB 0.05–0.10 mg/kg; ACTD 0.015–0.03 mg/kg; BLEO 0.1–0.25 units/kg						
VAB II	0.06 mg/kg day 1	0.5 units/kg/day day 1–7 continuous IV	0.02 mg/kg day 1	Platinum 1 mg/kg day 8	50	50	22
	Repeat every 3 months Maintenance: VLB, ACTD, BLEO weekly; Platinum replaces ACTD every 3 weeks						
VAB III	0.4 mg/m² day 1	200/m² day 1–7 continuous infusion IV	1 mg/m day 1	Platinum 120 mg/m² day 8; Cytoxin 600 mg/m² day 1	90	60	49
	Repeat every 4–5 months; Maintenance (21-day cycle): VLB 4 mg/m² every 3 weeks; chlorambucil 4 mg/m² day 1–14 PO; ACTD 1 mg/m²; Adriamycin 45 mg/m² alternate; Platinum 50 mg/m² every 3 weeks						

tween days 4 and 20 was frequently severe and dose-limiting. Pulmonary toxicity was observed in one patient.

The VAB II regimen [3] consisted of the following: bleomycin by IV invusion 0.5 mg/kg/day for 7 days, vinblastine 0.06 mg/kg and actinomycin D 0.02 mg/kg on day 1, and platinum 1 mg/kg on day 8. Maintenance was with vinblastine, actinomycin, and bleomycin once weekly, with platinum substituting for actinomycin every third week. The induction course was repeated 4 months after the start of therapy. Following this reinduction, maintenance was changed to vinblastine 0.1 mg/kg and actinomycin 0.025 mg/kg every 3 weeks and chlorambucil 0.1 mg/kg PO daily for a total of 2–3 years in the absence of relapse.

Of 50 patients treated with VAB II regimen, 25 (50%) achieved CR and 17 (34%) PR. Tumor shrinkage began within 2 weeks. The median duration of response was 13

Table 3. Actinomycin D, vincristine, and bleomycin in testicular cancer

Group	Actinomycin D	Vincristine	Bleomycin	No. evaluable points	Overall response	CR
Eastern Cooperative Oncology Group [2]	0.4 mg/m² day 1–5 Repeat every 3 weeks × 5 then every 30 days × 6;	1 mg/m² day 1, 8 then every 60 days	42	26	26 (69%)	8 (19%)
Southwest Oncology Group [14]	0.35 mg/m² day 1–4 every 3 weeks	1 mg/m²/week	15 units/m² twice weekly	20	12 (60%)	6 (30%)

months for the CR group but only 5 months for the PR group. In the CR group, 23 patients became free of measurable disease on chemotherapy alone; two additional patients had surgery at a later date because of residual disease after chemotherapy. At the time of the recent literature report, the median survival for the CR group has not yet been reached, with 11 patients still diesease-free at 16–33 months. All those not achieving CR had a median survival of only 8 months. In patients without previous chemotherapy the CR rate was 60%, with a median duration of 21 months. In those with prior drug treatment the CR rate was 40%, with only an 8-month median duration.

Nausea and vomiting caused by actinomycin and platinum were universal and lasted for at least 1–2 days, occasionally for as long as 1–2 weeks, especially after platinum. Mucositis and alopecia occurred in most patients. Fewer than 15% of the patients had a leukopenia value below 3,000, and all of these had had prior radiation and/or chemotherapy. Platelet counts of less than 100,000 were seen in only one patient. There were no cases of drug-related sepsis. Twenty percent of the patients had transient elevation of serum creatinine to less than 2.0 mg/m. There was one bleomycin-related death from progressive pulmonary insufficiency, occurring 5 deaths after an abdominal operation during which high oxygen concentration was used. A modest decrease in vital capacity by 10%–20% of the baseline value was common.

VAB III [2] consists of bleomycin given by continuous infusion (20 mg/m²), cyclophosphamide (600 mg/m²), and actinomycin D (1 mg/m²). High dose *cis*-platinum diammine dichloride (120 mg/m²) is given on day 8, with prehydration and a sustained mannitol diuresis. Maintenance with Velban (4 mg/m²) every 3 weeks and chlorambucil 4 mg/m² PO daily is given for 2 of every 3 weeks. Actinomycin D (1 mg/m²), adriamycin (45 mg/m²) and platinum (50 mg/m²) are alternated. The induction phase is repeated at 4–5 month intervals.

In 90 evaluable patients the CR rate is 60%, with 49% still. Showing no evidence of disease (NED) [6].

Two cooperative groups have looked at the combination of vincristine plus bleomycin with the addition of actinomycin (Table 3). In both cases the results were disappointing.

The Eastern Cooperative Oncology Group [2] has reported a study of Stage III testicular carcinoma in which patients were randomly assigned to treatment with actinomycin D (0.4 mg/m² IV on days 1–5), bleomycin (15 mg/m² IV on days 1, 8, 15), and vincristine (1 mg/m² IV on days 1–8), or to actinomycin D at the above dosage alone.

Of 102 patients entered on the study, 84 were evaluable. With actinomycin D alone 5/42 (12%) have achieved CR, compared with 8/42 (19%) on the combination. When PR status is looked at the combination is clearly superior, with 21/42 (50%) versus 4/42 (10%) for actinomycin D alone. The median duration of response is 27 weeks for the single agent and only 12 weeks for the combination; there is thus no meaningful clinical difference between these two regimens.

Einhorn [4, 5] has reported on 50 patients with germ-cell tumors of the testes, with metastatic measurable disease, treated with platinum 20 mg/m²/day for 5 days given as a 15-min IV infusion. The platinum was repeated every 3 weeks for three courses.

Vinblastine was given on days 1 and 2 in a total dosage of 0.4 mg/kg for a total of five courses and then given as a single injection in a dosage of 0.3 mg/kg every 4 weeks for a total of 2 years of therapy. Bleomycin 30 units IV was given on days 2, 9, and 16 of each platinum course, and was given with the platinum 6 h after the vinblastine and then weekly for a total of 13 weeks. The bleomycin was stopped at a total dosage of 350 units to minimize pulmonary fibrosis. "Fifty patients were studied initially. Thirty-three of 47 evaluable patients (71%) achieved complete remission. Only five of these 33 complete remissions have relapsed at the last report. In addition five of the 12 partial remissions were rendered disease-free following surgical removal of residual disease after significant reduction of tumor volume with chemotherapy."

The platinum caused moderate to severe nausea and vomiting in all patients during each 5-day course. Vigorous hydration has been used, 100 cm³ normal saline/h being given for 12 h before administration of drug and

Table 4. Vinblastine dosage

No prior therapeutic experience with radiation or other chemotherapy program		Prior exposure to radiation or other chemotherapy program	
Karnofsky	Vinblastine dose (days 1 and 2)	Karnofsky	Vinblastine dose (days 1 and 2)
K = 50%	0.13 mg/kg	K = 50%	0.11 mg/kg
K = 60%	0.14 mg/kg	K = 60%	0.12 mg/kg
K = 70%	0.15 mg/kg	K = 70%	0.13 mg/kg
K = 80%	0.16 mg/kg	K = 80%	0.14 mg/kg
K = 90%	0.17 mg/kg	K = 90%	0.15 mg/kg
K = 100%	0.18 mg/kg	K = 100%	0.16 mg/kg

then a continuous drip at 100 cm^3/h throughout the 5 days of the platinum dosing. With this approach biochemical manifestations of renal toxicity have been uncommon in Einhorn's experience.

Bleomycin in the regimen has produced fever, chills, and skin toxicity, none of which caused dose modification. All patients had significant alopecia and most had weight loss. The average witht loss was 20 lb. There was one death in the 50 patients from pulmonary fibrosis.

The most serious side effect was leukopenia, which was seen in all patients. The nadir was usually 1,000 between days 7 and 14. Eighteen patients required hospitalization for presumed sepsis with granulocytopenic fever. Seven had documented gram-negative sepsis and one of these patients died of sepsis.

Einhorn follows patients post-operatively once a month for the first year with chest X-rays and β-HCG and α-fetoprotein determinations. He feels this allows him to pick up relapse with minimal disease being present. In such patients he has achieved CR in 20/22.

With chemotherapy in the past, CR has been associated with cure, although the CR rate was not high. In some series, cure has been seen in 50% of these who achieved CR. In general, most relapses after CR have occurred within 2 years of initiation of therapy. This would bode well for an increased cure rate with the newer combinations.

There is now ample evidence that metastatic testicular cancer is potentially curable with aggressive combination chemotherapy. The regimens used are toxic and should only be administered by trained oncologists within a therapeutic setting of ample supportive care. It would seem realistic to approach metastatic testicular cancer at least as aggressively as acute myelocytic leukemia, where the cure potential is less. Physicians who diagnose testicular cancer should be sure to consult with, or refer to, oncologic treatment centers, so as to give every patient the optimal chance for salvage.

Recently at Stanford [7] an analysis was undertaken of the severe marrow toxicity that can result after vinblastine, bleomycin, and platinum. The analysis showed that severe marrow toxicity was strongly correlated with Karnofsky performance status and prior exposure to radiation. In view of this, a sliding scale of vinblastine dosage based on these two features has been developed (Table 4). This has been incorporated into a current Northern California Oncology Group protocol.

Anderson [1] has recently analyzed some of the prognostic variables for complete response to drug treatment, utilizing data from MD Anderson, Sloan-Kettering, University of Indiana, and Roswell Park (Table 5). Histology is a critical variable. The CR rate in embryonal carcinoma

Table 5. Prognostic factors for chemotherapy response (derived from [1])

Prognostic factor		No. of patients	No. CR	% CR
I	Histology	127	92	72.4
	1. Embryonal with or without seminoma			
	2. Teratocarcinoma	89	40	44.9
	3. Choriocarcinoma	20	8	40
	4. Extragonadal primary tumor	11	4	36.4
II	Tumor Burden			
	1. Non-bulky			
	A. Gynecomostia or elevated HCG	5	5	100
	B. Supraclavicular nodes	3	3	100
	C. Less than five pulmonary metastases (less than 2 cm in diameter)	39	33	84.6
	D. Above plus non-bulky nodes	32	24	75.0
	2. Bulky			
	A. > 5 pulmonary metastases (> 2 cm diameter)	40	22	55.0
	B. Large retroperitoneal nodes	39	21	53.8
	C. Visceral involvement	20	2	10

Table 6. Some unanswered questions in testicular cancer combination chemotherapy

1. Is vinblastine + bleomycin + platinum superior to vinblastine + bleomycin alone?
2. What is the optimal dose level of vinblastine?
3. Are bleomycin continuous infusions superior to IV push or IM schedules?
4. What is the optimal dose level and schedule of platinum?
5. What is gained by adding more drugs to vinblastine + bleomycin + platinum:
   a) Actinomycin D
   b) Actinomycin D + alkylating agent
   c) Actinomycin D + alkylating agent + adriamycin
6. What is the value of maintenance therapy after attainment of CR?

Table 7. Modern combination chemotherapy in testicular cancer

Group	Regimen	No. points evaluable	No. CR	% CR
Samuels et al.	VLB + BLEO	92	52	57
SWOG	VLB + BLEO	11	5	45
Memorial Hospital	VLB + BLEO + ACTD	68	15	22
Einhorn et al.	VLB + BLEO + PLAT	47	35	74
University of Leiden (18)	VLB + BLEO + PLAT	40	24	60
Memorial Hospital	VLB + BLEO + PLAT + ACTD	50	25	50
Memorial Hospital	VLB + BLEO + PLAT + ACTD + Cytoxan (CLB)	90	54	60
Memorial Hospital	VLB + BLEO + PLAT + ACTD + Cytoxan (CLB) + Adria	49	29	59

lesions, with or without seminoma elements, is 72.4%, as compared with only 44.9% in teratocarcinoma and 40% in choriocarcinoma. In extragonadal lesions the CR rate was also low at 36.4%. Another important prognostic variable is the tumor burden being treated. The CR rate was 84.6% (33/39) in patients with less than five pulmonary metastases less than 2 cm in diameter. In those with more extensive pulmonary metastases the rate dropped to 55% (22/40).

A variety of critical questions about the newer combination chemotherapy of testicular cancer remain unanswered (Table 6). These relate to the drugs used and their schedule intensity and duration. At this time no regimen can be recommended as clearly superior to all others. The three major drugs are vinblastine, bleomycin, and platinum. None of the regimens adding on actinomycin with or without alkylating agents and adriamycin have dramatically higher response rates than those reported for regimens without these drugs (Table 7). In fact, a trial comparing vinblastine plus bleomycin alone and with the addition of platinum has never been reported. As regards vinblastine, the ideal dose level still remains questionable. It does appear from ongoing studies of Einhorn and his group that lower doses can give equivalent or CR rate in their VBP regimen. What still remains to be determined is whether survival will be as good with the lower doses and whether better-risk patients are now being treated. Both the MD Anderson and the Sloan-Kettering groups feel that continuous infusions of bleomycin are superior to their earlier useage of the drug by IV push. Again, this can only be supported by historical controls and has to be measured against Einhorn's results without bleomycin infusions. Platinum is utilized on a range of schedules and dose levels, none of which can be established as definitive.

Testicular cancer raises some crucial questions about the adjuvant chemotherapy strategy. In testicular cancer curative chemotherapy is available when patients develop metastatic relapse after their initial local and regional control therapy. In such a situation the need for adjuvant chemotherapy becomes less urgent. Adjuvant chemotherapy will potentially increase the cure rate when added to the local control modalities of surgery and irradiation. It will do so, however, at the cost of treating some patients with drugs unnecessarily. What has to be compared in a clinical research setting is the cure rate of two therapeutic approaches. The first involves optimal treatment with surgery and/or irradiation followed by close observation. At the earliest sign of metastatic relapse curative intent chemotherapy will be used. In addition, surgical resection of isolated pulmonary metastases could be undertaken as indicated. The second approach would involve initial adjuvant chemotherapy and secondary salvage chemotherapy in those patients who relapse. Surgical resection of metastases could still be used as appropriate. A cost benefit ratio analysis will have to be made in comparing the two approaches. The benefit will be the overall cure rate. The cost will be the morbidity and mortality of therapy. It is important to realize that comparing the relapse-free survival of surgery against that obtained with surgery plus adjuvant chemotherapy will not be the crucial endpoint for analysis. It is conceivable that adjuvant chemotherapy will give a superior initial relapse-free survival rate but not be superior in terms of overall survival. In patients with Stage II disease at least half will be cured by their initial surgery. They will be receiving the costs of adjuvant chemotherapy without benefit. These costs involve not only the risks of physical morbidity and treatment mortality, but a range of psychosocial and economic costs, which must be considered as well.

The analysis of adjuvant drug trials in testicular cancer will therefore be a complex one involving a range of different endpoints and cost-benefit analysis. An initial endpoint will be relapse-free survival vs acute toxicity. The ultimate endpoint will be overall survival vs the acute and chronic toxicities of the treatment. These chronic toxicities will involve such aspects as long-term renal function and auditory function after *cis*-platin, neurologic function after vinca alkaloids, pulmonary function after bleomycin, and cardiac function after adriamycin. In addition, the incidence of second malignancies possibly due to treatment will need to be carefully monitored. It will be

Table 8. Mini-VAB regimen for adjuvant chemotherapy in good-risk Stage-II disease

Vinblastine Actinomycin D Bleomycin	0.06 mg/kg 0.02 mg/kg 0.25 mg/kg	weekly × 6
	↓ 2-week interval	
Actinomycin D Chlorambucil	0.02 mg/kg 0.1 mg/kg 1 day × 7	every 14 days for 1 year
	↓	
Actinomycin D Chlorambucil	0.02 mg/kg 0.1 mg/kg	every 21 days for 1 year

Table 9. Adjuvant chemotherapy after lymphadenectomy for Stage II disease at Memorial Sloan-Kettering Cancer Center

	Regimens		
	Good prognostic[a] features	Poor prognostic features	
	VAB I	VAB I	VAB III
Number of patients	33	29	22
Number relapsed	0	10	0
Median follow-up time	19+	25+	10+

[a] ≤ 5 involved lymph nodes none longer than 2 cm; no extralymphatic extension; negative markers

tempting, after early analysis of adjuvant trials in testicular cancer, to repeat positive results based on initial relapse-free survival. This temptation should be tempered by the realization that early actuarial analysis can be over-optimistic and that successful secondary salvage they may change the final picture dramatically.

At Sloan-Kettering [16] a modified, less toxic, version of VAB I (Table 8) was adminstered to 62 patients with Stage II disease who had undergone lymphadenectomy and had not received prior radiation. To date, 84% of the patients still remain disease-free. The most potent prognostic variable was found to be the extent of retroperitoneal lymph-node involvement. In 29 patients with bulky nodal disease or direct extranodal extension, relapses occurred in 10 (35%) after VAB I adjuvant treatment, after a median follow-up of 25+ months. Nine of these ten relapses occurred within 8 months of lymphadenectomy. In 33 patients with only microscopic involvement of the nodes none have relapsed, with a median follow-up of 19+ months. The features that make for good prognosis Stage II in the Sloan-Kettering experience are ≤ 5 involved lymph nodes, none larger than 2 cm in diameter, no direct extralymphatic extension, and negative tumor markers after lymphadenectomy.

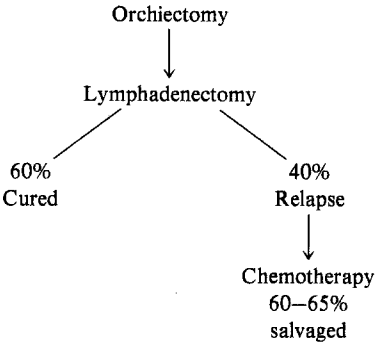

Fig. 1. A perspective on adjuvant chemotherapy of testicular cancer. Expected salvage rate for sequential surgery and drugs in stage II testicular carcinoma

The VAB I experience indicated that a strategic split was indicated for Stage II patients. Those with good prognostic features could continue on the modified VAB I regimen, but those without those features required more aggressive adjuvant chemotherapy. Therefore 22 Stage II patients with poor prognostic signs were then given the more aggressive VAB III regimen after lymphadenectomy. All 22 patients have remained disease-free for a median duration of 10+ months (Table 9).

It has been estimated that patients with pathologically documented Stage II disease after lymphadenectomy have a 40% relapse potential. This means that 60% of the patients would receive the risks of adjuvant chemotherapy without possibly having any benefit. The chemotherapy data available would indicate that in the 40% of patients who would relapse after lymphadenectomy about 60%–80% could be expected to achieve CR with drugs, with 60% of the entire group showing long-term disease-free survival indicative of cure. Thus, surgery with delayed chemotherapy at the time of relapse could be expected to salvage 85% of all patients (60% initially plus 25% at relapse) (Fig. 1). To show a 10% improvement with surgery plus immediate adjuvant chemotherapy would require 210 patients in a clinical trial. Even if this 10% improvement in cure rate were obtained, it would be necessary to weight this against the cost of 60% receiving the risks of drug unnecessarily. Currently, a national study has been set up in the United States, in which many of the major cooperative groups will participate and pool their patients. In this study adjuvant chemotherapy in Stage II with resectable lymph nodes will be compared to an initial therapeutic approach which eradicates all known disease (surgery), followed by monthly observation of the patient and institution of potentially curative chemotherapy in those patients who develop recurrence. Excluded from this study will be patients whose markers remain abnormal 4 weeks after lymph node resection and

Table 10. Two adjuvant regimens utilized in the testicular cancer intergroup study

Vinblastine	–15 mg/kg IV days 1 and 2 every 4 weeks for 8 weeks	4 mg/m^2 day 1 and 29
Bleomycin	30 units (total weekly dose) IV weekly for 8 consecutive weeks	30 mg IV push then mg/m^2/24-h infusion 6 days repeated every 28 days
Platinum	20 mg/m^2 IV daily for 5 days once every 4 weeks for two courses	120 mg/m^2 days 7
Actinomycin D	–	1 mg/m^2 days 1 and 2
Cyclophosphamide		600 mg/m^2 days 1 and 2

those whose retroperitoneal nodes are clinically or surgically unresectable. The groups participating in this study will have a choice of two chemotherapy regimens. One is a modified VBP regimen and the other is a modified VAB III regimen (Table 10). As can be seen, these two regimens overlap in the usage of vinblastine, bleomycin, and platinum, but the dosage schedules differ significantly. In addition, the VAB adds actinomycin D and cyclophosphamide. In both approaches only two cycles of adjuvant chemotherapy are given.

When relapse occurs in either of two protocol arms, four cycles of the same regimen used as adjuvant are to be administered. In the group that has received two adjuvant cycles the "reinduction" is modified as to the amount bleomycin and in the VBP arm the dose of vinblastine is lowered to 0.3 mg/kg every 4 weeks.

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