Treatment of Advanced Seminoma with Dactinomycin, Cyclophosphamide, Vinblastine, Bleomycin and Cis-Platinum (The Vab-6 Protocol)

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Summary

Eighteen patients with advanced seminoma (stages IIc—III) were treated with: cytoxan 600mg/m², vinblastine 4mg/m², actinomycin D 1mg/m², bleomycin 30mg, i.v. on day 1, followed by bleomycin 30mg/day by infusion, days 1-3, and cis-platinum 120mg/m² on day 4. 9/18 pts. achieved complete remission and have been followed clinically; no recurrences have occurred in this group. The other 9 pts. had residual masses after 3 cycles of chemotherapy; they were taken to surgery and no viable tumor was found on surgical specimens. There were 3 recurrences in this group, always distant from the site of original disease. These patients were successfully treated with salvage chemotherapy and radiotherapy. One of these patients died of hepatic failure unrelated to his seminoma. All the other patients are alive, at a median follow-up of 50 months. This chemotherapy regimen is effective in curing advanced seminoma.

Uniterms: *seminoma chemotherapy; advanced seminoma*

Although the prognosis of patients with pure seminoma in stage I (disease confined the testis) and early stage II (few retroperitoneal limph nodes) remains excellent with conventional radiotherapy, the same cannot be said about patients with bulky abdominal disease (stage IIc) or extra-abdominal disease (stage III). For these patients, radiotherapy yields much poorer results, with a high relapse rate and 5-year survival figures in the range of 20% or less for most of the reported series.

Advances in the chemotherapy of non-seminomatous testicular cancer (NSTC) throughout the last decade have made these tumors consistently curable. Several chemotherapy regimens containing cis-platinum, vinblastine and bleomycin as basic drugs have been developed and significantly increased the cure rate of disseminated NSTC. Paralelling the application of these protocols to disseminated NSTC, we[1] and several others[2,3,4,5,6,7] have used chemotherapy in treating disseminated seminoma. It soon became clear that seminomatous tumors are at least as sensitive — if not more sensitive — to chemotherapy than NSTC. Table I summarizes some of the international experience with cis-platinum containing chemotherapy in advanced seminoma.

Table I — Results of chemotherapy regimens in advanced seminoma.

Author	Protocol	Nº Patients	Results
Simon et al. (1983)	VAB-6	10	100% *
Morse et al. (1983)	VAB-6	22	82% *
Oliver (1984)	PVB	12	83% *
Van Oosterom (1984)	PVB	73	70% §
Stanton et al. (1985)	VAB-6	30	86% §
Friedman et al. (1985)	PVB	20	90% §

* *disease-free survival* § *initial CR*

We report here the results of treatment of 18 patients with advanced seminoma with a slightly modified VAB-6 protocol and propose guidelines for the treatment strategy of such patients.

Material and methods

Between August 1980 and July 1984, eighteen patients with advanced (stages IIc-III) testicular semino-

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ma were treated. All patients had had no prior chemotherapy. Patients were staged with physical examination, chest roentgenogram, abdominal computerized tomography, serum markers (alpha-fetoprotein and beta-HCG in all patients, LDH in most patients) and rarely with bipodal lymphangiography. Patients characteristics are shown in Table II.

Table II — Patients characteristics

Age	**31 (median); 25-52 (range)**
Previous-chemotherapy	0/18
Previous para-aortic radiotherapy	5/18
Previous mediastinal radiotherapy	3/18
Elevated AFP	0/18
Elevated beta-HCG	6/18
Elevated LDH	4/10
Massive intra-abdominal disease	14/18
Pulmonary disease	3/18
Massive supra-clavicular/cervical disease	1/18

Patients were treated with 3 cycles of chemotherapy and submitted to surgical resection of residual masses about 4 weeks after the completion of chemotherapy. No maintenance chemotherapy was given.

The first 13 patients received classical VAB-6 chemotherapy: dactinomycin 1mg/m^2, cyclophosphamide 600mg/m^2, vinblastine 4mg/m^2 and bleomycin 30mg were given intravenously on day 1, followed by a continuous bleomycin infusion (30mg/day) from day 1 through day 3 and cisplatinum 120mg/m^2 with saline infusion and mannitol-induced diuresis on day 4. Cycles were repeated 21-28 days apart, depending on blood counts. Bleomycin was ommitted on the third cycle.

The last 5 patients were treated with an adaptation of this protocol for outpatient use, as previously reported by us[8].

Surgical resection of residual masses was carried out 4-6 weeks after completion of chemotherapy. Low concentration of inspired oxygen (maximum 28%) was used during surgery because of previous exposure to bleomycin. All patients were rendered free of disease after the operation. No further chemotherapy was given after surgery.

Results

All patients attained a complete remission (CR) after 3 cycles of chemotherapy. In 9/18 patients there was clinical CR, shown by physical examination, x-rays, abdominal CAT scan and serum markers. These patients received no further treatment and were followed clinically. With a median follow-up of 47 months (range 36-83 months) none of these patients has relapsed. Of interest was the extremely rapid decrease of tumor masses seen after the start of chemotherapy, with complete responses seen at the end of the first cycle of therapy in most cases. In patients with abdominal pain due to tumor there was complete relief of pain within 12-24 hours from start of therapy.

In 9/18 patients there was evidence of residual tumor mass after 3 cycles of therapy. These were all abdominal masses. These 9 patients were taken to surgery and complete removal of the residual masses was accomplished in all cases. None of these patients had histological evidence of viable tumor in the surgical specimens, which showed necrosis and fibrosis only. Of significance was the fact that extensive fibrosis was present in the retroperitoneum of these patients, which precluded effective lymphadenectomy in some cases[9]. With a median follow-up of 54 months (range 38-76 months) there have been 3 relapses in this group, at 5, 5 and 8 months after surgery for removal of residual masses. One patient had a relapse in the supra-pubic area and the other 2 patients had hepatic recurrences. These 3 relapses occurred in areas previously uninvolved by disease. The 3 patients with recurrent disease were re-treated with a combination of VP-16-213 and cisplatinum for 4 cycles, followed by radiotherapy to the affected areas (2,500 r). Two of these patients are alive at 76 and 60 months, with no evidence of disease. The third patient died at 49 months of hepatic failure following blood transfusion-related cirrhosis of the liver. He had no evidence of disease at autopsy.

Toxicity

Despite the apparent aggressiveness of this protocol, toxicity was considered mild to moderate. Nausea and vomiting were universal but this was dramatically ameliorated with the introduction of high-dose metoclopramide and dexamethasone. Total alopecia was seen in 16/18 patients. Chemical phlebitis was seen in 4/18 patients. Leukopenia of moderate degree (leukocytes below 2,000/mm^3, granulocytes below 1,200/mm^3) was seen regularly. There were 7 febrile episodes requiring antibiotics. None of these had a documented site of infection or positive blood cultures. Mild elevation of serum creatinine (up to 2,8mg/ml) was seen in 2 cases and reverted to normal with further saline hydration. Ototoxicity consisting of mild hearing loss and tinnitus was reported by 2 patients. This symptoms subsided in both patients after a few months. One patient had a "idiosyncratic" reaction with the first cycle of chemotherapy, consisting of severe arthralgias, abdominal pain, fever, paresthesias in the lower limbs and an acute dermatitis. This patient received no further VAB-6 chemotherapy and on surgery was found to have had complete necrosis of his residual tumor. This patient went on to develop hepatic recurrence of his disease

and was re-treated successfully with VP-16 and cisplatinum without significant toxicity. This same patient developed clinically significant hypocalcemia after the first cycle of chemotherapy, requiring oral and intravenous calcium supplementation. There were no treatment-related deaths.

Toxicity data is summarized in table III.

Table III — Toxicity of VAB-6 chemotherapy in seminomas

	Nº Patients
Alopecia (complete)	16/18
Nausea	18/18
Vomiting (3 episodes/cycle)	14/18
Phlebitis	4/18
Sepsis	7/51 cycles
Renal failure (transient, mild)	2/18
Hearing loss (transient)	2/18
Hypocalcemia, symptomatic	1/18
"Idiosyncratic" reaction	1/18
Treatment-related deaths	0/18

Discussion

Our data shows a remarkable sensitivity of seminomas to chemotherapy. This is in agreement with other data in the literature also showing an initial CR to chemotherapy in excess of 80%.

Our data shows that the concept of "high-risk" patients — as defined by any of the current definitions — does not apply to patients with disseminated seminomas of testicular origin. All our patients would have been considered "high-risk" by current criteria; nonetheless, all of them showed an initial CR to chemotherapy.

We question the value of post-chemotherapy resection of residual masses in seminomas. This procedure, which is of value both therapeutically as well as in assessing the need for further treatment in cases of non-seminomatous tumors, proved to be of no value in our seminoma patients. It had no therapeutic value (all our relapses occurrences occurred far from the residual necrotic masses), nor had it value in assessing the need for further treatment (all the resected specimens showed only necrosis and fibrosis). This finding seems to be in agreement with other data from the literature[10,11].

The role of radiotherapy is also questioned. Pre-chemotherapy radiotherapy in advanced seminoma should be definetely discouraged, since it is not only ineffective in most cases but also increases the risk of life-threatening leukopenia should chemotherapy be needed in case of treatment failure.

Post-chemotherapy radiation therapy, as recommended by some authors[12] routinely in the treatment of advanced seminoma seems also unecessary. Our series show that only had the original tumor masses no viable tumor cell after chemotherapy but also that relapses occurred far from the initial site of disease.

Our experience shows that the treatment of advanced seminoma should always be started with chemotherapy. Our proposed regimen is extremely effective in inducing complete remissions and we recommend 3 cycles of therapy as optimal treatment. Residual tumor masses need not be irradiated nor resected, but should be monitored closely, without treatment. Further treatment will be indicated only if there is evidence of progression of disease.

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