Improved Management of the Advanced Nonseminomatous Testis Cancer

DAVOR VUGRIN

Supported in part by grant CA-05826 from NIH, and private fund from E. and L. Sorkin

From: *Solid Tumor Service, Department of Medicine*
Memorial Sloan-Kettering Cancer Center, New York, N.Y., 10021, USA

Requests for reprints: *Davor Vugrin, M.D.*
Comprehensive Cancer Center
Duke University Medical Center
Durham, N.C., 27710, USA

ABSTRACT

With the VAB-6 program about 90% (54/59) of patients with stage III and bulky stage II disease achieved complete remission and eighty percent remain free of disease. Patients with minimal metastatic disease can usually be treated successfully with chemotherapy alone, while patients with advanced disease frequently required combined treatment with chemotherapy and surgery in order to achieve complete remission. Most patients without a teratomatous component in the testis tumor will achieve complete remission with chemotherapy alone, whereas patients with a teratomatous component are more likely to require the combined approach of chemotherapy and surgery to achieve disease free status. Pure seminoma was apparently the most responsive and pure choriocarcinoma the least responsive histologic type of testis tumor to the combination chemotherapy. The incidence of a residual mature teratoma in the resected specimem has increased with the improved efficacy of chemotherapy. High complete remission rates and a short duration of treatment ensure rapid return of afflicted individuals to productive life, thus, fulfilling a most important goal of treatment.

Malignant germ cell tumors of the testis although rare, represented until recently, one of the most common causes of cancer death in the 19 – 34 year age group, and thus produced a significant social, economic and psychologic impact.[1] In this report, progress achieved in the chemotherapy of these neoplasms at Memorial Sloan–Kettering Cancer Center is summarized.

Nonseminomatous germ cell tumors of the testis (NSGCTT) account for approximately 60% of germ cell tumors and have always represented a greater therapeutic challenge than seminomas.[1,2] Analysis of newly diagnosed patients with NSGCTT presenting at MSKCC between 1975 and 1978 revealed that malignancy was clinically confined to the testis in 38% (79/208) (stage I), to the testis and retroperitoneal lymph nodes in 41% (86/208) (stage II), and beyond the retroperitoneal lymph nodes in 21% (43/208) (stage III).[3] Treatment in stages I and II in the USA has been primarily surgical and has achieved cure rates of 85% and 50 – 60%, respec-

tively.[4] Although hope for cure of disseminated germ cell tumors was raised by chemotherapy in 1960,[5] a dramatic improvement in survival in stage III disease was not seen until the incorporation of cis diammine dichloroplatinum (II) (cis platinum, CDDP), vinblastine, and bleomycin into chemotherapy combinations in the mid seventies.

The goal of chemotherapy is cure without intolerable toxicity and production of complete remission (CR) is an essential first step. In pursuit of this goal, since 1972, at MSKCC, six consecutive combination chemotherapy regimens were evaluated in the treatment of disseminated nonseminomatous germ cell tumors of the testis.[6,13] In first three programs, with a successive and rational incorporation of an increasing number of individually active drugs and changes in the drug schedules, complete remission rates increased from 15% with VAB-1 (three drugs: vinblastine, actinomycin D, bleomycin) to 60% with the VAB-3 (seven drug combination: vinblastine, actinomycin D, bleomycin, cis diamminedichloroplatinum, cyclophosphamide, adriamycin, chlorambucil).[6,8] This experience determined that induction incorporating cyclophosphamide, actinomycin D, vinblastine, bleomycin infusion, and high dose cis platinum was the most effective part of the VAB chemotherapy regimen. Therefore, after VAB-3, qualitatively similar inductions have been given at progressively shorter intervals.[8,13] Although the apparent initial CR rates to the subsequent chemotherapy regimens have been similar (60%) repeated inductions at shortened intervals have resulted in more effective sterilization of maligant elements. This enabled and additional 20 – 30% of patients, primarily those with bulky metastatic deposits at the beginning of chemotherapy, to become free of disease after resection of residual tumor and additional chemotherapy.[9,16] Until late 1978, patients were treated with the VAB-4 and VAB-5 protocols for 2 1/2 years.[9,10] However, the increased effectiveness of induction regimens diminished the importance of prolonged maintenance chemotherapy and led to the development of the VAB-6 regimen.[11,13] VAB-6 consists of 3 – 4 successive chemotherapy inductions given 3 – 4 weeks apart (table 1). Each induction requires 4 days of chemotherapy giving cyclophosphamide, vinblastine, bleomycin and actinomycin D by intravenous push on the first day, followed immediately by 3 days of continuous bleomycin infusion, and high dose cisplatinum over 20 – 30 min. with Mannitol induced diuresis on the fourth day. Incomplete responders after 3 inductions or those with initially bulky retroperitoneal metastastases are explored one month after the 3rd induction with intent to resect residual disease. If the resected tumor contains malignant elements, an additional 2 inductions are given. Complete responders to the first 3 chemotherapy inductions and those in whom only mature teratoma is found in resected residual tissue receive no additional inductions. The first 25 patients so treated received a brief maintenance to complete 1 year of chemotherapy. Complete remission was achieved in 23 of 25 (92%) of evaluable patients, 80% of whom remain in remission with a median follow up of 36 + months.[11] Because of the excellent results of the VAB-6 regimen and the lack of an increased relapse rate with the reduction of maintenance in the latter experience, maintenance has been omitted completely in subsequent experience.[12] Thirty one of 34 (91%) evaluable patients achieved complete remission and 28 remain free of disease with median follow up of 24 + months.[13] Thus with the VAB-6 program about 90% (54/59) of patients achieved complete remission, ***roughly*** 60% (35/59) with chemotherapy alone and 30% (19/59) with combined chemotherapy and surgery. In patients who achieved complete remission with combined chemotherapy and surgery the resected specimen consisted of mature teratoma in two thirds and of malignant elements in the one third. Eighty percent of patients treated with the VAB-6 regimen remain continuously free of disease with median follow up of over two and half years.

Patients with minimal metastatic disease can usually be treated successfully with chemotherapy alone, while patients with advanced disease frequently require combined treatment with chemotherapy and surgery in order to achieve complete remission.[11,13] Of 22 patients with minimal metastatic deposits who were treated with the VAB-6 program, 18 (82%) achieved complete remission with chemotherapy alone, and an additional 4 patients after resection of residual disease (total CR 100%). Of patients with advanced disease, 16 (43%) achieved CR with chemotherapy alone, and an additional

15(41%) became free of disease after resection of residual disease (total CR 84%). Patients having only pulmonary metastases had higher CR rates subsequent to chemotherapy alone, than patients with concomitant pulmonary and retroperitoneal disease. The reason for this is not clear but the often bulkier nature of metastases in the retroperitoneum may be one of the reasons.

Pure seminoma was apparently the most responsive (CR 6/6) histologic type of germ cell tumor to the VAB-6 regimen despite the fact that such patients had massive metastatic deposits.[11,13,17] Lower complete remission rates with chemotherapy alone were observed in patients with equally bulky nonseminomatous disease (CR seminoma vs NSGCT = 100% vs < 30%, respectively). Most patients without a teratomatous component in the primary tumor will achieve CR with chemotherapy alone, whereas patients with a teratomatous component are more likely to require the combined approach of chemotherapy and surgery to achieve disease free status.[11,13] Embryonal carcinoma shows high CR rates to chemotherapy alone.[8,13] Pure choriocarcinoma remains the least responsive histologic type of gonadal germ cell tumor and 30 of 32 patients with pure choriocarcinoma seen at MSKCC during the last 3 decades were dead within a median of 4 months despite various forms of chemotherapy.[18] 80% of patients with pure choriocarcinoma develop brain metastases.[19] However, choriocarcinoma occuring in association with other germ cell elements has a better prognosis. Choriocarcinoma elements were present in 24% (28/118) of patients with stage III or bulky stage II disease in whom VAB-4, VAB-5, or VAB-6 was the first chemotherapy. CR was achieved in 21/28 with and in 74/88 without choriocarcinoma elements, and 21 (76%), respectively, remain in Cr.

Over the past few years progressively larger numbers of patients with stage III or bulky stage II neoplasm have entered complete remission with the help of adjunct surgery after initial chemotherapy.[8,16] Response to chemotherapy, proper timing of surgery, and complete resection of residual tumor are essential for success. Surgical resection of a tumor that is progressing inspite of chemotherapy is usually unsuccessful due to inability to resect tumor completely, or due to the emergence of metastases in other locations. Patients in whom residual malignant disease is completely resected are the major beneficiaries of the combined approach. Six of the 9 VAB-6 patients in whom malignant elements were completely resected remain free of disease. All received an additional two VAB-6 inductions to prevent the recurrence associated with prior programs. All these patients would have relapsed without resection and, indeed, the disease progressed in those who had no resection or who had incomplete resection of residual malignant disease.

Pulmonary metastases have a high CR rate to chemotherapy alone (CR 75 – 90%) and thoracotomy will render an additional 10% free of disease after resection of residual neoplasm.[9,13,20] Up to one half of patients achieving CR of thoracic metastases with chemotherapy will have residual retroperitoneai tumor.[20] The outcome of treatment of such patients will be influenced by the response of retroperitoneal metastases to chemotherapy and the ability to resect residual deposits completely.

The indications for retroperitoneal lymph node dissection following chemotherapy for stage III disease in those without prior lymphadenectomy have not been clearly defined. Our limited experience suggests that most patients with clinically minimal retroperitoneal lymph node metastases achieve CR with chemotherapy alone.[16] However, CR of retroperitoneal deposits with chemotherapy alone was achieved in only 24% (12/49) of patients with bulky nonseminomatous retroperitoneal metastases. An additional 43% (21/49) became free of disease following resection of residual metastases.[16] The resected tissue was mature teratoma in 60% and malignant tumor in 40% of these patients. We recommend that patients with bulky retroperitoneal metastases have RPLND after 3 chemotherapy inductions because of the low CR with chemotherapy alone, because resection of teratoma and of malignant elements can convert an incomplete response to a CR, and because the pathologic findings help determine the need for further chemotherapy.

The incidence of mature teratoma in the resected specimen has increased with the improved efficacy of chemotherapy.[6,13] The role of chemotherapy in "inducing" evolution of less differentiated tumors to mature teratoma is not clear. The possibilities are that chemotherapy destroys the malignant stem cell (embryonal carcinoma) leaving on-

ly mature differentiated elements, or that chemotherapy itself induces differentiation of undifferentaited tissues, or that chemotherapy promotes patient survival permitting "spontaneous differentiation". The natural history of chemotherapy associated mature teratoma without resection is not clearly defined because the histologic diagnosis can only be made on resected tissue.

Serum tumor markers, alpha feto-protein (AFP) and human chorionic gonadotrophin (HCG), in conjuction with other clinical evaluations, are useful in staging, in planning therapy and in prognosis.[21] Patients with stage III tumors and elevated AFP alone or in association with HCG had lower CR rates (40%) with chemotherapy alone although significant number (15/30) became free of disease following resection of residual disease.[11,13] Very high (> 1000 ng/ml) serum concentrations of AFP or HCG were associated with specially poor complete responses to chemotherapy, possibly because of large tumor burdens.[21]

Serum tumor markers during treatment generally parallel the responseto chemotherapy and become normal in those who achieve CR. However, in patients receiving intensive chemotherapy, tumor marker abnormalities may resolve despite clinical or radiographic evidence of residual tumor and despite negative serum tumor markers, 11/38 (29%) patients operated after chemotherapy had residual malignant tissue.[14] In fact, serum tumor markers were negative after initial chemotherapy in 55% (11/20) of all patients with documented residual malignancy. The absence of elevated serum tumor markers was associated with high complete resection rates.[14] All patients with elevated serum tumor markers, preoperatively, had residual malignant disease and in only 1/11 was complete resection possible. Thus, persistent marker elevation consitutes a relative contraindication to exploration and the patient with such a finding should be reinduced or treated with a new program.

Potentially serious and life threatening side effects may occur following induction. Myelosupression has been the most common potentially serious side effect. Roughly 15% of the VAB-6 patients received broad spectrum antibiotics when they developed fever duriong myelosuppression. No patient treated with VAB-6 experienced serious acute or chronic renal toxicity. Nausea and vomiting from cis platinum and actinomycin D can be successfully treated with repeated injections of combined pentobarbital (100 mg IM) and chlorpromazine (25 mg IM). Mucositis, a major debilitating toxicity with prior VAB regimens did not occur with the VAB-6 regimen or was mild. Pulmonary fibrosis was not observed.

The experience with the VAB-6 regimen suggests that about 90% of patients with advanced disease will achieve complete remission and that maintenance may not be necessary. High CR rates and a short duration of treatment ensure rapid return of afflicted individuals to productive life, thus, fulfilling a most important goal of treatment.

REFERENCES

1. *Cancer Patient Survival.* Report No. NIH: 77-992, U.S. Department of Health, Education, and Welfare, Washington, D.C., 1976.
2. BATATA, M.A.; UNAL, A. — *The role of radiation therapy in relation to stage and histology of testicular cancer.* Semin. Oncol., 6:69-81, 1979.
3. BREDAEL, J.J.; VUGRIN, D.; WHITMORE, W.F., Jr. — *Selected Experience With Surgery and Chemotherapy in the Treatment of Nonseminomatous Testis Tumors.* J. Urol., (in press).
4. WHITMORE, W.F., Jr. — *Surgical treatment of adult germinal testis tumors.* Semin. Onc., 6:55-68, 1979.
5. LI, M.C.; WHITMORE, W.F.; GOLBEY, R.B., et al. — *Effects of combined drug therapy on metastatic cancer of testis.* J. Amer. Med. Assoc., 174:1291-1299, 1960.
6. WITTES, R.E.; YAGODA, A.; SILVAY, O., et al. — *Chemotherapy of germ cell tumors of the testis. 1. Induction of remission with vinblastine, actinomycin D, and bleomycin.* Cancer., 37:637-645, 1976.
7. CHENG, E.; CVITKOVIC, E.; WITTES, R.E., et al — *Germ cell tumors (II): VAB II in metastatic testicular cancer.* Cancer., 42:2162-2168, 1978.
8. REYNOLDS, T.F.; VUGRIN, D.; CVITKOVIC, E.; CHENG, E.; BRAUN, D.W.; O'HEIR, M.A.; DUKEMAN, M.E.; WHITMORE, W.F., Jr.; GOLBEY, R.B. — *VAB-3 Combination Chemotherapy of Metastatic Testicular Cancer.* Cancer., 48:888-898, 1981.
9. VUGRIN, D.; CVITKOVIC, E.; WHITMORE, W.F., Jr.; CHENG, E.; GOLBEY, R.B. — *VAB-4 Combination Chemotherapy in the Treatment of Metastatic Testis Tumors.* Cancer., 47:833-839, 1981.
10. VUGRIN, D.; WHITMORE, W.F., Jr.; GOLBEY, R.B. — *VAB-5 Combination Chemotherapy in Prognostically Poor Risk Patients With Germ Cell Tumors.* Cancer., (in press).
11. VUGRIN, D.; HERR, H.W.; WHITMORE, W.F., Jr.; SOGANI, P.C.; GOLBEY, R.B. — *VAB-6 Combination Chemotherapy in Disseminated Cancer of the Testis.* Annals. Int. Med., 95:59-61, 1981.
12. VUGRIN, D.; HERR, H.; SOGANI, P.; WHITMORE, W.; GOLBEY, R. — *VAB-6 Without Maintenance: Progress in Chemotherapy of Testicular Germ Cell Tumors (GCT).* Proc. Amer. Soc. Clin. Oncol., 22:474, 1981.
13. VUGRIN, D.; WHITMORE, W.F., Jr.; GOLBEY, R.B. — *VAB-6 Combination Chemotherapy Without Maintenance in Treatment of Disseminated Cancer of the Testis.* Cancer., (in press).
14. VUGRIN, D.; WHITMORE, W.F., Jr.; SOGANI, P.C.; BAINS, M.; HERR, H.W.; GOLBEY, R.B. — *Combined Chemotherapy and Surgery in Treatment of Advanced Germ Cell Tumors.* Cancer., 47:2228-2231, 1981.
15. VUGRIN, D.; WHITMORE, W.F.; GOLBEY, R.B. — *Effect of Shorter Induction Intervals on Complete Remisson (CR) Rates in Advanced Nonseminomatous Germ Cell Tumors of Testis (NSGCTT).* Proc. Amer. Assoc. Cancer. Res., 23:148, 1982.

16. VUGRIN, D.; WHITMORE, W.F., Jr.; HERR, H.; SOGANI, P.; GOLBEY, R.B. — *Indication for Retroperitoneal Lymph Node Dissection (RPLND) After Chemotherapy for Advanced Nonseminomatous Germ Cell Testis Cancer (NSGCT).* Proc. Amer. Soc. Clin. Oncol., 1:113, 1982.
17. VUGRIN, D.; WHITMORE, W.; OCHOA, M.; GOLBEY, R. — *Cis diamminedichloroplatinum (II) (CDDP) in combination chemotherapy of metastatic seminoma.* Proc. Amer. Assoc. Canc. Res. (Canc. Res.), 22:166, 1981.
18. WHITMORE, W.F., Jr.; VUGRIN, D.; GOLBEY, R. — *Prognostic Significance of Choriocarcinoma Elements in Testis Cancer.* Proc. Amer. Soc. Clin. Oncol., 1:115, 1982.
19. VUGRIN, D.; CVITKOVIC, E.; POSNER, J.; HAJDU, S.; GOLBEY, R.B. — *Neurological Complications of Malignant Germ Cell Tumors of the Testis: Biology of Brain Metastases.* Cancer., 44:2349-2353, 1979.
20. VUGRIN, D.; WHITMORE, W.F., Jr.; BAINS, M.; GOLBEY, R.B. — *Role of Chemotherapy and Surgery in the Treatment of Thoracic Metastases from Nonseminomatous Germ Cell Testis Tumors.* Cancer., (in press).
21. FRIEDMAN, A.; VUGRIN, D.; NISSELBAUM, J.; GOLBEY, R. — *Prognostic Significance of Serum Tumor Biomarkers (TM), Alpha Feto Protein (AFP), Beta Subunit of Human Chorionic Gonadotrophin (bHCG), and Lactate Dehydrogenase (LDH) in Nonseminomatous Germ Cell Tumors (NSGCT).* Proc. Amer. Soc. Clin. Oncol., 21:323, 1980.