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Vinblastine, Bleomycin and *Cis*-diamminedichloroplatinum in Disseminated Testicular Cancer: Response to Treatment and Prognostic Correlations

A Southwest Oncology Group Study*†

M. K. SAMSON,‡ R. FISHER,§ R. L. STEPHENS,|| S. RIVKIN, ¶ M. OPIPARI,** T. MALONEY†† and C. W. GROPPE‡‡

‡*Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan* 48201, *U.S.A.*, §*M. D. Anderson Hospital and Tumor Institute, Department of Biomathematics, Houston, Texas* 77030, *U.S.A.*, ||*University of Kansas Medical Center, Kansas City, Kansas* 66103, *U.S.A.*, ¶*The Tumor Institute of Swedish Hospital Medical Center, Seattle, Washington* 98104, *U.S.A.*, **Department of Medical Oncology and Hematology, Detroit Osteopathic Hospital, Detroit, Michigan* 48203, *U.S.A.*, ††*Wilford Hall USAF Medical Center, Lackland AFB, Texas* 78236, *U.S.A. and* ‡‡*Cleveland Clinic Foundation, Cleveland, Ohio* 44106, *U.S.A.*

Abstract—*One-hundred and forty-three patients with advanced germinal cell neoplasms of the testis were treated with a* 4-month *induction chemotherapy regimen of vinblastine, bleomycin and* cis-*diamminedichloroplatinum. Subsequent maintenance therapy for responding patients consisted of chlorambucil and actinomycin-D, alternating monthly with vinblastine. The duration of maintenance therapy was* 20 months. *Eighty-four patients* (59%) *entered into complete remission while* 34 *patients* (24%) *were partial responders. To date,* 76% *of patients in complete remission are relapse-free at* 1 yr *and* 68% *are relapse free at* 2 yr.

Significant leukopenia ($<3000/mm^3$) *was observed in over* 50% *of evaluable courses: thrombocytopenia* ($<100{,}000/mm^3$) *in* 18% *of courses. Major non-hematologic toxicities included renal, gastrointestinal, dermatologic and neuromuscular.*

Several prognostic factors were analyzed to determine the effect on complete remission rate, remission duration and survival. The most important parameters included histology, tumor burden, pre-treatment performance status and marrow reserve. Other important factors were pre-treatment level of HCG and LDH, histology and solitary site of metastatic disease. These factors should be incorporated in the design of future clinical trials.

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Reprint requests to: Southwest Oncology Group (SWOG) Operations Office, Rainbow Blvd., Suite 100, Kansas City, Kansas 66103, U.S.A.

INTRODUCTION

WHILE testicular tumors, with an estimated incidence of 2.2 per 100,000 patients, comprise only 1–2% of male malignancies, they constitute the leading cause of death by cancer in men between the ages of 29 and 35 [1, 2]. Thus, by striking young men in their prime of life, the psychological impact of the disease is considerable.

In 1960, Li *et al.* published the first account of combination chemotherapy in metastatic testicular cancer [3]. Following this report,

numerous investigators modified Li's original schedule and/or drug combination in an attempt to improve the response rate [4–7]. Although these studies were only able to achieve 10–30% complete remissions, about one half of the complete responders were long term survivors and represent chemotherapy 'cures'.

Samuels *et al.*, as well as others, pioneered the next major advance in the chemotherapy of testicular neoplasms—the introduction of the vinblastine–bleomycin regimen, resulting in a significant improvement in complete remission rate [8–10].

In the early 1970's, *cis*-diamminedichloroplatinum (NSC-119875, DDP) entered into clinical trial. It was quickly recognized to be particularly active in germinal neoplasms, with an overall response rate in testicular cancer in excess of 60%, making it the most active single agent in this disease category [11]. A Phase I study at Wayne State University demonstrated that DDP could be safely combined with vinblastine and bleomycin [12]. A number of studies have now been published, namely those of Einhorn *et al.* and the sequential VAB reports from Golbey *et al.*, employing these three drugs with schedule modifications [13–14].

In April 1976, the Southwest Oncology Group (SWOG) initiated a Phase II study of vinblastine, bleomycin and DDP (VBP) in advanced testicular cancer. A preliminary report of this study has already been published [15]. What follows is an evaluation of this study 12 months after its close, with particular emphasis on the following prognostic factors: tumor burden, bone marrow status, performance status, age, histology, pre-treatment serum lactic dehydrogenase (LDH), human serum chorionic gonadotropin (B_2HCG), prior surgery, prior radiotherapy and metastatic pattern.

MATERIALS AND METHODS

All eligible patients had advanced, histologically proven carcinoma of germ cell origin, with clearly measurable metastatic disease and/or an elevated serum beta subunit of HCG. Additional eligibility criteria included: no prior exposure to any of the chemotherapeutic agents utilized in this study, the absence of central nervous system metastases, an absolute granulocyte count $>1000/mm^3$ and platelet count $>100{,}000/mm^3$ normal renal function defined as a BUN <20 mg%, a serum creatinine $\leqq 1.2$ mg%, a creatinine clearance $\geqq 75$ ml/min with no evidence of obstructive uropathy and adequate pulmonary function defined as a vital capacity or FEV_1 $>70\%$ of predicted. Patients with pure seminoma were eligible provided there was evidence of extranodal metastatic disease or documented failure of radiation therapy. Pretreatment evaluation included complete history and physical examination, performance status,* hemogram, 17-channel screening profile, serum beta subunit HCG, alpha fetoprotein, chest X-ray with whole lung tomograms, i.v. pyelogram, serum creatinine and creatinine clearance, audiogram and pulmonary function tests. Brain, bone and liver scans were performed when clinically warranted. While on study, hematologic and roentgenographic evaluations of each patient were performed at at least monthly intervals. Response duration and survival curves were prepared using Gehan's test [16].

Drug regimen

Treatment schema is shown in Table 1. Vinblastine, bleomycin (total dose of $200\ U/m^2$) and DDP were administered over the initial induction period of 4 months. Careful attention to maintenance of fluid bal-

Table 1. *Treatment schema*

Induction therapy (4 months)		
Drug	Dose	Days of treatment
Vinblastine	$12\ mg/m^2$	1, 29, etc.
Bleomycin	$15\ U/m^2$	BIW until total dose of $2000\ U/m^2$ is reached
DDP	$13\ mg/m^2$	1–5, 29–33, etc.
Maintenance therapy (20 months)		
Actinomycin D	$1.5\ mg/m^2$	1, 58, etc.
Chlorambucil	$10\ mg/m^2$ p.o.	4–8, 61–66, etc.
Vinblastine	$12\ mg/m^2$	29, 87, etc.

*Performance status criteria: grade 0, fully active, able to carry on all predisease activity without restriction; grade 1, resricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; grade 2, ambulatory and capable of all self-care but unable to carry out any work activities: grade 3, capable of only limited self-care, confined to bed or chair $>50\%$ of walking hours: grade 4, completely disabled.

ance was requested of all investigators, but a mannitol-induced diuresis and pre-management hydration were left to the discretion of the managing physician. Patients in complete or partial remission at the completion of induction therapy received maintenance therapy consisting of chlorambucil and actinomycin-D, alternating monthly with vinblastine, for an additional 20 months. Chemotherapy was discontinued after a total of 24 months of treatment and then patients were followed until evidence of clinical relapse. Those patients who had received extensive prior irradiation received a 25% reduction in dose of vinblastine. Each subsequent treatment course was administered provided there was sufficient evidence of recovery from the nadir leukocyte and platelet count observed with the previous course of therapy. DDP was withheld if there was evidence of nephrotoxicity (creatinine >1.3 mg%, BUN >30 mg%) and was reinstituted once baseline values were reached. Bleomycin was permanently discontinued if pulmonary toxicity developed, manifested either by pulmonary infiltrate or a decrease of 25% or greater in pre-treatment pulmonary function.

Response criteria

Responses were classified as follows:

1. Complete remission (CR): complete disappearance of measurable disease and symptoms for a minimum of 4 weeks and normalization of tumor markers, if initially elevated.
2. Partial remission (PR): greater than 50% but less than 100% reduction in the sum of the areas of all measurable lesions, for a minimum of 4 weeks.
3. Progression: more than 50% increase in the sum of the areas of all measurable lesions and/or the appearance of new lesions.
4. Relapse: appearance of new lesions or reappearance of old lesions in patients who had achieved complete remission, including tumor markers. For patients in partial remission, an increase of 50% or more of the sum of the products of the diameters of the measured tumors over that which was obtained at the time of maximum regression during partial remission. The starting point for calculating response duration was the earliest date recorded which documented that particular response.

Table 2. WHO Classification of testicular germ cell tumors*

A. Tumors showing a single cell type
1. Seminoma
2. Embryonal carcinoma
3. Yolk sac tumor
4. Teratoma
5. Choriocarcinoma
B. Tumors showing more than one histologic pattern
1. Embryonal + teratoma ± seminoma
2. Embryonal carcinoma + seminoma
3. Teratoma + seminoma
4. Any combination with choriocarcinoma

*World Health Organization.

Patient population

The 143 patients had a median age of 27 yr (mean 29, range 15–80). Eighty-five per cent of patients had an initial performance status of 0–1. All tumors were categorized histologically by the World Health Organization (WHO) classification (Table 2). Table 3 enumerates the nature of prior therapy as well as sites of metastatic disease in this treatment population.

Table 3. Patient population

Prior treatment	No. of Patients
Orchiectomy alone	81
Orchiectomy + lymphadenectomy	30
Orchiectomy + lymphadenectomy + radiation therapy	5
Orchiectomy + radiation therapy	15
Other	12
Metastatic sites	
Lung (including mediastinum and hilar lymph nodes)	89
Lymph nodes	63
Liver	12
Other (bone, skin, etc.)	24

RESULTS

Response to therapy

All eligible patients entered into this study who received at least 1 day of therapy, were considered evalable for response. Of these 143 patients, there were 84 complete remissions (59%) and 34 partial remissions (24%) for an overall response rate of 83%. Table 4 illustrates responses by histologic type, for both pure as well as mixed histologic groups. The

Table 4. Response rate

WHO classification	No. of patients	Complete remissions	Partial remissions	No. of CR relapses
Seminoma	8	2 (25)*	1 (13)	2 (100)
Embryonal carcinoma	61	45 (74)	11 (18)	8 (18)
Teratoma	6	2 (33)	2 (33)	1 (50)
Choriocarcinoma	3	1 (33)	1 (33)	0
Teratocarcinoma	32	16 (50)	10 (31)	4 (25)
Embryonal carcinoma + any other type	9	5 (56)	3 (33)	1 (20)
Teratoma + seminoma	2	1 (50)	0	1 (100)
Choriocarcinoma	22	12 (55)	6 (27)	3 (25)
Totals	143	84 (59)	6 (24)	20 (24)

*Numbers in parentheses are percentage of total.

median time to CR was 12 weeks (range 3–64) with 20 patients achieving a CR status during maintenance chemotherapy. To date, 20 patients in complete remission (24%) have relapsed, 16 in anatomic regions of previously documented disease, and four in new areas, including two patients who developed central nervous system metastases. Overall, 76% of patients were relapse-free at 1 yr and 68% at 2 yr after achieving a complete remission, as calculated by the life table method. Median duration of remission was greater than 147 weeks (range 11–147+) for complete responders with 23 patients presently beyond 2 yr in duration of their remission. Figure 1 illustrates survival duration of patients by the maximum response achieved. These differences in survival depending on the best response achieved are all statistically significant ($P=0.001$).

Eighteen patients underwent surgery at the completion of the four courses of induction therapy, because of persistent abnormalities on physical examination, X-rays or scan. In three patients no active tumor was found but rather fibrosis, reactive hyperplasia or necrotic debris. In five patients (three of whom the original diagnosis was embryonal cell carcinoma and remaining two teratocarcinoma) mature teratoma was noted, and completely removed. These eight patients are considered to have achieved a disease-free status and are included with those patients categorized as complete responders. In the remaining 10 patients active tumor was found at surgery and, although all gross tumor was removed, these patients are considered to have reached a partial remission status for purposes of this evaluation.

Hematological toxicity

Median nadir of leukopenia observed during induction therapy was 3000 mm^3 (range $0.5–9.9 \times 10^3$) and median nadir of thrombocytopenia was 170,000/mm^3 (range 25–400 $\times 10^3$). There was no evidence to suggest cumulative bone marrow toxicity with succeeding courses of treatment. Significant leukopenia ($<3000/mm^3$) was noted in 58% of evaluable courses and significant thrombocytopenia ($<100{,}000/mm^3$) in 18%. No appreciable hematologic toxicity was noted during maintenance therapy. One patient died of a leukopenic-related pneumonia and was considered to be a toxic drug death.

Non-hematologic toxicity

Nausea and vomiting were reported to be present in 42% of patients, alopecia in 17%, dermatologic toxicity in 15%, fever in 17%, neuromuscular toxicity in 10% and stomatitis in 10%. The frequency of altered pulmonary function attributable to bleomycin did not exceed 5% of patients; however, one patient developed progressive pulmonary insufficiency secondary to bilateral pulmonary fibrosis after receiving a total dose of bleomycin of 200 U/m^2.

In 20% of the patients, BUN was noted to rise above 20 mg%, while in 23% serum creatinine was above 2.0 mg%. Only one patient developed serum creatinine exceeding 4.0 mg%. An attempt was made to assess the effect of DDP on renal function by serial evaluation of serum creatinine and creatinine clearance values correlated with courses of therapy during induction and maintenance therapy. Our results indicate a tendency for an average drop in creatinine clearance of 11 ml/min at or after the 6th course of therapy with a 95% confidence interval of 2–20 ml/min.

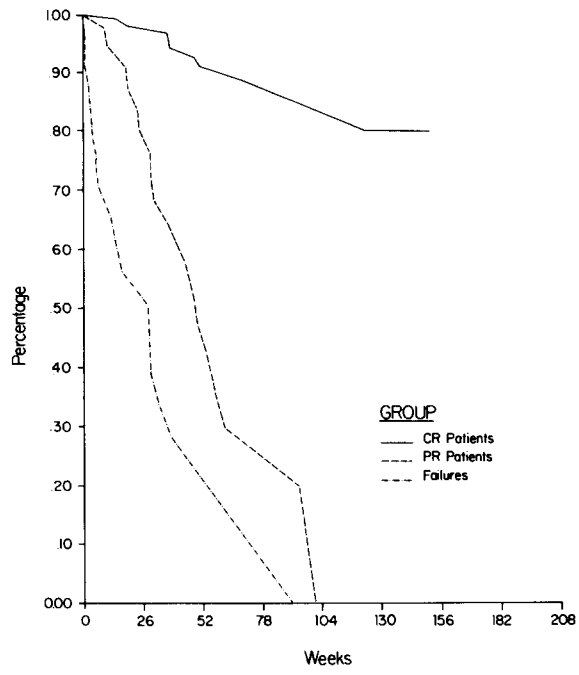

Fig. 1. Survival (weeks) *of patients: complete vs partial vs non-responders* (P=0.001).

Tinnitus was noted in only eight patients; however, clinically appreciable hearing loss was not recorded.

Prognostic variables

Ten prognostic variables were examined to determine the effect, if any, there was on complete remission rate, duration of complete remission and survival duration: age (<35 vs >35), bone marrow status, bulk of disease, performance status, histology, prior surgery, prior radiotherapy, pre-treatment LDH and HCG, and metastatic pattern.

Bulky disease was defined as having at least one of the following characteristics: (1) five or more pulmonary metastases, each greater than 2 cm in diameter; (2) large retroperitoneal metastases; and (3) visceral metastases (liver, bone, etc).

The following metastatic patterns were utilized in the analysis: lung only; lymph nodes only; liver only; lung, liver and lymph nodes; lung and liver; and lung and lymph nodes.

The nature of previous surgery included: diagnostic only (orchiectomy) and curative (orchiectomy and retroperitoneal lymphadenectomy).

Pre-treatment LDH values were divided into two categories: greater than 3 × institutional norms, and less than 3 × institutional norms.

Beta subunit HCG values were divided into two groups: greater than 1000 mi.u. ml and less than 1000 mi.u. ml.

Complete remission rate

The complete remission rate for those patients classified as having bulky disease was 49% (50/103) while for those patients with non-bulky disease an 85% complete remission rate (34/40) was noted. For those patients with performance status 0–1 a 67% CR rate was observed; for patients with a performance status of 2–4 only 19% entered into complete remission. Both of these differences, bulky vs non-bulky and performance status 0–1 vs 2–4 were statistically significant (P<0.001).

Other factors with significant bearing on CR rate were: (1) histology (embryonal alone vs all other histologies, $P=0.002$); (2) LDH (<3 × normal versus >3 × normal, $P=0.027$); (3) HCG (<1000 mi.u./ml vs >1000 mi.u./ml, $P=0.028$); (4) metastatic pattern (lung only vs all others, $P=0.001$) single site vs multiple sites, $P=0.011$).

When one compares histologies, adjusting for tumor burden, differences in complete response rate between embryonal carcinoma (±seminoma) (61% of whom had bulky disease) vs all other combinations (82% with bulky disease) continued to be statistically significant ($P=0.037$).

Patients classified as having adequate bone marrow reserve had a higher complete response rate (61%) than patients with inadequate bone marrow reserve (38%). This difference was almost statistically significant ($P=0.059$).

CR duration

Significant factors affecting CR duration were marrow status with a 1-yr relapse-free rate of 78% for adequate marrow reserve patients and 40% relapse-free rate for inadequate marrow reserve patients ($P=0.021$) and bulk of disease with non-bulky and bulky disease patients having an 87% and 68% 1-yr relapse-free rate, respectively ($P=0.047$).

Complete response duration was longer for patients with a single site of metastases than those with multiple sites of metastases, and almost reached statistical significance at the $P=0.05$ level.

Survival

Significant factors affecting survival are: (1) marrow status ($P=0.003$, Fig. 2); (2) tumor

burden ($P=0.003$, Fig. 3); (3) and performance status ($P=0.001$, Fig. 4). For survival comparison between seminoma, embryonal cell carcinoma and teratocarcinoma, there

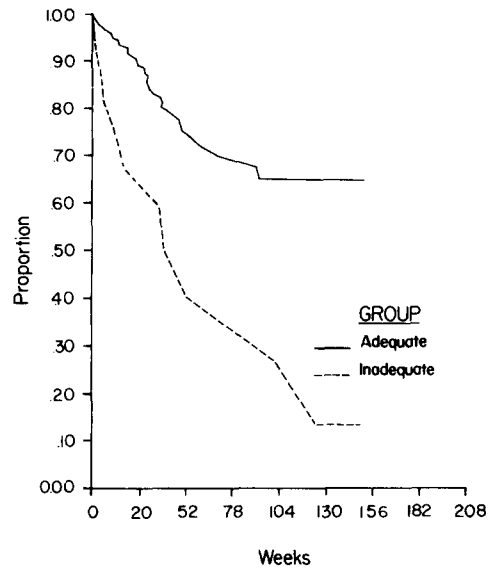

Fig. 2. Survival (weeks) *of patients: adequate vs inadequate bone marrow status* (P=0.003).

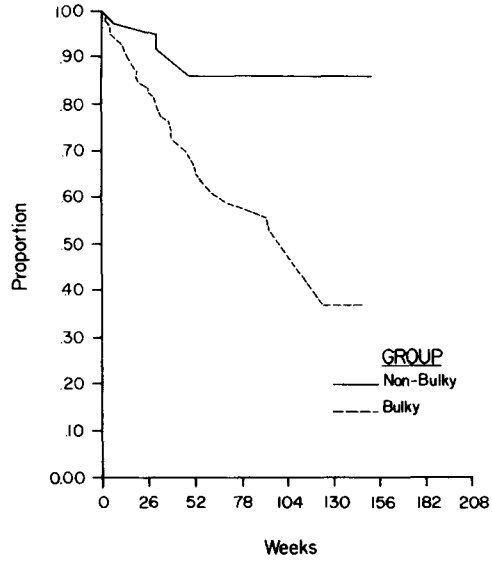

Fig. 3. Survival (weeks) *of patients: bulky vs non-bulky disease* (P=0.003).

was a clear survival advantage of the latter two groups over the former ($P=0.006$) with 1 yr survival of 16, 76 and 73% respectively. Patients who had undergone more extensive surgery prior to entry into the study had longer survival ($P=0.022$, Fig. 5), as well as patients with solitary versus multiple sites of metastatic involvement ($P=0.012$, Fig. 6).

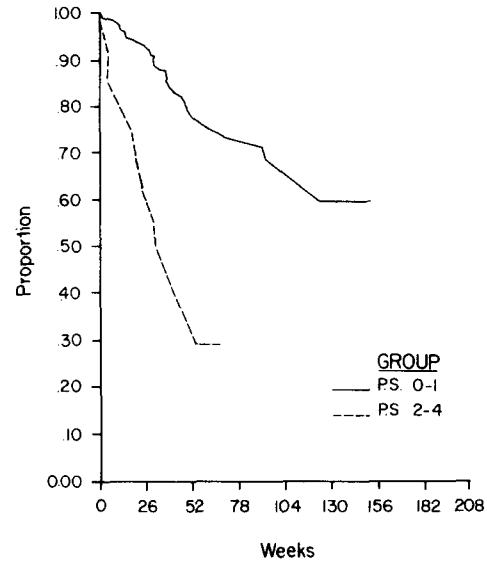

Fig. 4. Survival (weeks) *of patients: performance status* 0–1 vs 2–4 (P=0.001).

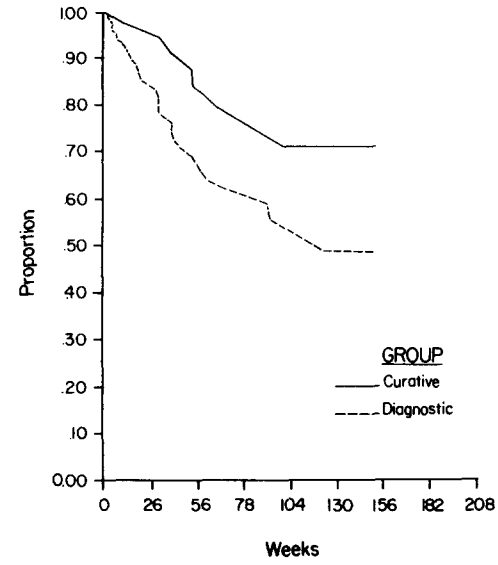

Fig. 5. Survival (weeks) *of patients: curative surgery vs diagnostic only* (P=0.022).

DISCUSSION

Since the introduction of DDP into clinical trials of advanced testicular germ cell malignancies, considerable progress in the treatment of this malignancy has been made. Past clinical studies were able to induce complete responses with chemotherapy and a small percentage of long term disease-free survivors. More recent trials, incorporating DDP, have increased both complete response rate and disease-free survival beyond

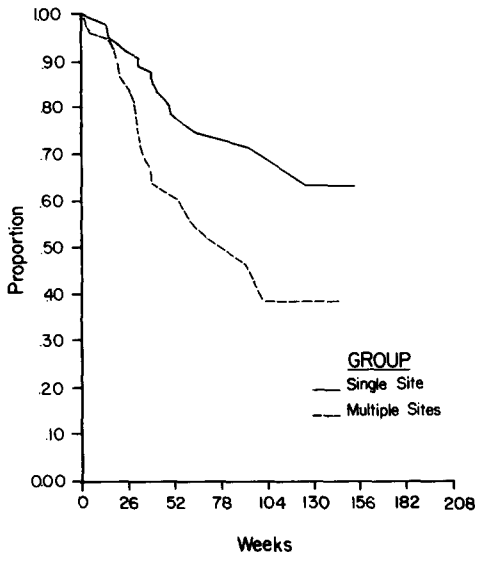

Fig. 6. Survival (weeks) *of patients: single vs multiple sites of metastases* (P = 0.012).

2 yr, an interval of time generally considered to be tantamount to cure.

Our study, representing the contribution of a large multi-institutional cooperative group, again confirms the high degree of activity of the combination of vinblastine, bleomycin and DDP (VBP) when utilized as an induction regimen. The large number of patients entered into this study has enabled us to evaluate the effect of several prognostic factors with respect to complete response rate, duration of complete response (disease-free interval) and survival.

As Samuels *et al.* [9] previously reported, the major determinant in predicting complete response appears to be tumor burden. For those patients classified as having bulky disease, a 49% CR rate was achieved, while in those patients with non-bulky disease (28% of all patients in this study) an 85% CR rate was observed and is in line with other large series. Performance status proved to be an important prognostic factor with those patients with performance status of 0–1 achieving a 67% CR rate while for those with 2–4 performance status only 19% reached a CR status. Patients with pure embryonal cell carcinoma had a statistically significant higher CR rate than those with other histologies. This difference was maintained despite adjusting for bulk of disease, other factors influencing a higher CR rate including pre-treatment LDH $< 3 \times$ normal. HCG < 1000 mi.u. ml. and a solitary site of metastases all reflect a lower initial tumor burden.

Of the 20 patients who achieved CR status and then relapsed, 16 had pre-treatment bulky disease, and four had non-bulky disease. The median time to relapse from the point of entering CR was 20 weeks for both groups with a range of 6–49 weeks. The CR relapse rate for bulky disease patients was 32% (16/50) vs 12% (4/34) for non-bulky patients. This difference was statistically significant ($P < 0.03$). Two of the relapses occurred in the brain alone, a finding that suggests that the central nervous system represents a pharmacologic sanctuary.

Not suprisingly, a significant survival advantage for complete responders was found when compared to partial responders and those patients who failed to respond. However, even in those patients who entered a PR, median survival was 50 weeks and is markedly longer than that which was observed in the pre-DDP era. In addition to a complete response, other factors with significant bearing on durations of survival were: adequate pre-treatment bone marrow status, non-bulky tumor burden, good initial performance status, prior extensive surgery and solitary sites of metastatic disease. Age was found not to have a significant influence on CR rate, CR duration or overall survival.

In our series, five patients were found at surgery to have mature teratoma, following four months of induction chemotherapy. None of these patients has relapsed to date, suggesting this finding may be an additional favorable prognostic sign. This phenomenon has been documented in previous reports [17–19] and may represent treatment induced: (1) selective killing of malignant cells in a mixed cell-type population, (2) evolution of malignant cells into a benign-appearing tumor or (3) an inherent property of the neoplasm itself. The incidence of this occurrence is not known at the present time, but no doubt, will be noted in future studies.

We were not able to document any clinically significant decrease in renal function, as measured by creatinine clearance, beyond 10 ml/min, by the sixth course of therapy.

However, we must caution interpretation of these results as they are based on a limited data base available to us. Obviously, long term effects of platinum on renal function needs to be monitored as a majority of patients represent potential cures.

A significant step forward has been made in the treatment of advanced germ cell tumors of the testis with the incorporation of DDP into chemotherapy combinations. Current trials

are addressing: (1) the timing of 'debulking surgery'; (2) the adjuvant therapy of 'high risk' stage II non-choriocarcinoma patients; (3) the potential dose–response relationship of DDP; (4) the most active drug combination to be used in induction therapy; (5) the role, if any, maintenance chemotherapy serves in the management of this group of malignancies; and (6) salvage programs for non CR patients after induction chemotherapy.

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