*Europ. J. Cancer.* Vol. 17, No. 4, pp. 443–441, 1981
Printed in Great Britain

0014–2964/81/040433-09 $02.00/0


# The Treatment of Advanced Testicular Carcinoma with High Dose Chemotherapy and Autologous Marrow Support*

G. BLIJHAM,† G. SPITZER,‡§|| J. LITAM,‡ A. R. ZANDER,‡ D. S. VERMA,‡ L. VELLEKOOP,‡ M. L. SAMUELS,‡ K. B. McCREDIE‡ and K. A. DICKE‡

†*Department of Medicine, Annadal Hospital, Analaan 1, Maastricht, The Netherlands,* ‡*Department of Developmental Therapeutics, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute,* 6723 *Bertner Avenue, Houston, TX* 77030, *U.S.A.*

**Abstract**—*Thirteen patients with disseminated nonseminomatous germ cell carcinoma, failing to respond to extensive prior chemotherapy including* cis-*platinum, were treated with high dose chemotherapy. Cyclophosphamide* (4.5 g/m$^2$) *and epipodophyllotoxin* (VP-16) (600 mg/m$^2$) *were given followed by autologous bone marrow transplantation. In some cases* 1,3 *bis* (*β-chloroethyl*)-1-*nitrosourea* (*BCNU*), *adriamycin or platinum were also administered. Of* 10 *patients evaluable for response* 9 *responded;* 4 *patients achieved a complete remission and* 3 *a partial remission. Median response duration was* 15 weeks (*range* 4 *to* 20+ weeks). *Four patients died from treatment-related infections;* 2 *of whom entered the program already with fever and* 3 *of whom died after hematopoietic recovery. Major toxicities were bacterial and fungal infections. In patients treated with cyclophosphamide and VP-*16 *only, no fever was seen in* 3 *out of* 9 *courses. Granulocyte transfusion was given in only* 1 *of* 9 *courses. Neutrophils recovered to greater than* $1.5 \times 10^9$/liter *by day* 18–35 (*median* 23) *and platelets greater than* $100 \times 10^9$/liter *by day* 16 *to* 42+ (*median* 21). *Further experience with high dose cyclophosphamide and VP-*16 *followed by autologous bone marrow transplantation is needed to evaluate its value in the management of patients with disseminated nonseminomatous germ cell tumor failing front line conventional chemotherapy.*

## INTRODUCTION

RECENTLY, chemotherapy has greatly improved the outlook of patients with disseminated nonseminomatous testicular cancer. The two most widely used programs, the vinblastine–bleomycin combination developed by Samuels [1] and vinblastine–bleomycin–platinum regimen introduced by Einhorn *et al.* [2, 3], achieve complete remission rates of 40% and 70%, respectively. Moreover, more than 50% of the complete responders appear to be long-term survivors [3].

Accepted 2 October 1980.
*Supported in part by grant CA-23077 from the National Institutes of Health, Bethesda, Maryland.
§Scholar of the Leukemia Society of America, Inc.
||Request for reprints should be addressed to: Dr. Gary Spitzer, M. D. Anderson Hospital and Tumor Institute, Departmental of Developmental Therapeutics, 6723 Bertner Avenue, Houston, TX 77030, U.S.A.

The treatment of patients failing front-line chemotherapy has been considerably less successful. Most of the published studies include few or no patients previously treated with vinblastine–bleomycin with or without platinum [4–7]. The survival of patients that have failed the most successful chemotherapeutic agents is generally less than 1 year. Hence, there is a need to develop new strategies for this group.

In previous studies we and others [8–10] have shown that patients failing conventional treatment can obtain responses with high dose chemotherapy followed by autologous bone marrow transplantation to ameliorate the myelosuppression side effects. For obvious reasons, the most useful drugs in this setting are those (i) whose main side effect, even in high doses, is myelosuppression and (ii) those drugs with anti-tumor activity in conventional doses without evidence that the dose effect plateau has been reached [9]. In the case of testicular

carcinoma, cyclophosphamide [11] and VP-16 [12], and possibly the nitrosoureas [8], fulfil these criteria.

Therefore we started a phase I–phase II study to determine the toxicity as well as therapeutic efficacy of high dose cyclophosphamide and VP-16, in some cases in combination with other agents, followed by autologous bone marrow rescue in patients with refractory disseminated testicular carcinoma. Preliminary results in some of these patients have been reported earlier [8].

## MATERIALS AND METHODS

*Patient population*

Thirteen patients were included in the study. Patient age, performance status, histology, stage and marker status at diagnosis and at the time of entry on this program are given in Table 1. The median age was 26 years and the range 22–39.

The histological diagnosis in all patients was embryonal cell carcinoma, with 6/13 having seminomatous elements and 2/13 also having teratomatous elements. One patient, patient 12, presented with an extragondal mediastinal primary tumor. At the time of presentation for high dose chemotherapy, 12 of 13 patients had progressive Stage III (staging according to Maier [13]) with lung and/or liver metastases; one patient only had disease confined to the retroperitoneum.

*Prior chemotherapy and response*

Data on prior chemotherapy, response and duration of response to prior chemotherapy are given in Table 2. It is important to note that (i) the most successful chemotherapeutic regimen in these 13 patients produced only three complete remissions, (ii) with one exception, all responding patients had relapsed within one year, (iii) 10 patients were treated with vinblastine–bleomycin–platinum combinations resulting in only one complete remission and (iv) some patients on conventional doses of cyclophosphamide and VP-16 had progressive disease.

*Chemotherapy administration and dose*

Table 3 details the chemotherapy doses given to each patient. Patients 1–6 received cyclophosphamide plus VP-16 (CV) alone, generally in total doses of 4.5 g/m$^2$ and 600 mg/m$^2$, respectively, these doses being divided over 3–4 days. Patients 7–10 received CBV, cyclophosphamide, BCNU and VP-16, generally in total doses of 6 g/m$^2$, 300 mg/m$^2$ and 600 mg/m$^2$, respectively. Miscellaneous drug regimens were administered to patients 11–13, this being cytoxan and VP-16 (CV) plus adriamycin in patient 11, CV plus platinum in patient 13, and two different chemotherapy combinations in patient 12. Six of the ten eligible patients received a second course of megadose chem-

*Table 1. Patient characteristics*

| Patient number | Age | At presentation for ABMT program: Histology | Stage at diagnosis | Performance status | Extent of disease | AFP | Beta HCG |
|---|---|---|---|---|---|---|---|
| 1 | 39 | ECC | I | 1 | Lung | + | + |
| 2 | 32 | ECC+Sem | II | 1 | Lung, Liver, Retro | + | + |
| 3 | 26 | ECC | III | 0 | Lung | ND | ND |
| 4 | 33 | ECC | III | 1 | Lung | + | + |
| 5 | 27 | ECC+Sem+Ter | I | 0 | Lung | + | + |
| 6 | 28 | ECC+Sem+Ter+Ch | II | 0 | Retro | + | + |
| 7 | 28 | ECC | II | 2 | Liver, Retro | + | + |
| 8 | 21 | ECC | II | 4 | Liver, Retro | + | + |
| 9 | 22 | ECC+Sem | II | 4 | Lung, Liver, Retro+Brain | ND | ND |
| 10 | 22 | ECC | III | 1 | Lung, Liver | ND | ND |
| 11 | 22 | ECC+Sem | III | 1 | Lung, Liver, Retro | ND | ND |
| 12 | 22 | ECC | III | 3 | Lung, Retro | ND | + |
| 13 | 25 | ECC+Sem | II | 0 | Lung | + | + |

+, Elevated; ND, not done; ECC, embryonal cell carcinoma; Retro, retroperitoneum; Ch, choriocarcinoma; Ter, teratomatous elements; Sem, seminomatous elements; AFP, alpha fetal protein; Beta HCG, beta human chorionic gonadotropin.

*Table 2. Prior chemotherapy and response to prior chemotherapy*

| Patient number | Pretreatment with platinum: Regimen | Response | Duration (months) | Other chemotherapy | Duration of chemotherapy (months) | Exposure and response: CTX | VP-16 |
|---|---|---|---|---|---|---|---|
| 1 | V/B/P | NR | — | CTX/A/VCR/AD | 9 | +PR | — |
| 2 | V/B/P | PR | 13 | CTX/A/VCR/AD | 20 | +NR | — |
| 3 | V/B/P | PR | 2 | CTX/A/VCR/ AD/MTX/MC | 12 | +NR | — |
| 4 | V/B/P | PR | 6 | — | 7 | — | — |
| 5 | V/B/P | PR | 10 | VP-16 | 14 | — | +PR |
| 6 | V/B/P | CR | 5 | A/VP-16 | 14 | — | +NR |
| 7 | V/B/P | <PR | 4 | AD/Mit/May | 12 | — | — |
| 8 | VCR/B/P /AD | NR | — | V/B/CML | 10 | — | — |
| 9 | — | — | — | V/B/CTX/A/MTX/FU | 6 | +NR | — |
| 10 | P | NR | — | V/B/CTX/VCR /MTX/FU | 12 | +NR | — |
| 11 | V/B/P | <PR | 4 | — | 5 | — | — |
| 12 | V/B/P | PR | 4 | CTX/MTX/FU | 10 | +NR | — |
| 13 | CTX/A/P | PR | 3 | V/B | 15 | +NR | — |

CR, Complete remission; PR, partial remission; NR, no response; V, vinblastine; B, bleomycin; P, *cis*-platinum (CDDP); AD, actinomycin D; A, adriamycin; VCR, vincristine; CTX, cyclophosphamide; MTX, methotrexate; MC, mitomycin C; Mit, mithramycin; May, maytansin; CML, chloroambucil; FU, 5 fluorouracil.
Patient No. 13 = CR on V/B, duration 4 months.
Patient No. 10 = CR on V/B, duration 4 months.

*Table 3. Response to megadose chemotherapy*

| Patient number | Treatment: CTX ($g/m^2$) | VP-16 ($mg/m^2$) | Other ($mg/m^2$) | Number of courses | Response | Duration (weeks) | Treatment-related deaths |
|---|---|---|---|---|---|---|---|
| 1 | 3.9 | 600 | — | 1 | Early death | — | Yes |
| 2 | 4.0 | 500 | — | 1 | PR | 4 | No |
| 3 | 6.0 | 600 | — | 1 | <PR | 14 | No |
| 4 | 5.2 | 600 | — | 2 | CR | 16 | No |
| 5 | 4.5 | 600 | — | 2 | PR | 5 | No |
| 6 | 4.5 | 500 | — | 2 | PR | 20+ | No |
| 7 | 3.8 | 750 | B : 375 | 2 | CR | 5 | Yes |
| 8 | 6.0 | 600 | B : 300 | 1 | Early death | — | Yes |
| 9 | 6.0 | 800 | B : 300 | 1 | Early death | — | No |
| 10 | 6.0 | 600 | B : 300 | 2 | CR | 15 | No |
| 11 | 4.5 | 500 | A : 80 | 1 | NR | — | Yes |
| 12 | 6.0 | 450 | B : 300 | 2 | <PR | 4 | No |
| 13 | 3.9 | 600 | P : 100 | 1 | CR | 20 | No |

CR, complete remission; PR, partial response; <PR, less than partial response; P, platinum; CTX, cyclophosphamide; VP-16, epipodophyllotoxin; B, BCNU; A, adriamycin.
Patient 4 first course without transplant = CTX 3.9 $g/m^2$, VP-16 450 $mg/m^2$.
Patient 12 second course = adriamycin 100 $mg/m^2$, VLB 4.5 $mg/m^2$, Bleomycin 30 $mg/m^2$.

otherapy plus autologous transplant; in three of the other four, infectious complications were to preclude a second course.

*Supportive measures*

Some patients received intravenous alimentation, depending on performance and nutritional status. When patients became febrile, they were treated with antibiotics. When the fever did not respond to adequate antibiotic coverage within 48 hr, leukocyte transfusions from family members were added. Fungal

infections were treated with amphotericin B or miconazole. Platelet transfusions were used prophylactically when platelet counts were less than $20 \times 10^9$/liter. All allogenic blood products were irradiated with 2599 rads prior to transfusion to prevent possible graft-versus-host reactions.

*Definition of response*

Complete remission (CR) was defined as a complete disappearance of all evidence of tumor at all sites of tumor involvement. Partial response (PR) was defined as a decrease of >50% in the product of the largest perpendicular diameters of all measureable disease. A less than partial response (<PR) was evaluated to gain as much information on activity as possible, and was defined as a >25% reduction but less than 50% reduction of one or more sites of tumor involvement without progression elsewhere. Patients showing a less than 25% change in measurable disease were considered to have no response (NR).

*Bone marrow aspiration, dosage and transfusion*

An approximate volume of 1500 ml was aspirated from both posterior iliac spines and crests, collected, processed and frozen as described previously [8, 14]. At the time of infusion, the ampoules were removed from the storage tank, rapidly thawed, diluted, washed and infused as described previously [8, 14]. All patients were premedicated intravenously with 50 mg of diphenhydramine hydrochloride (Benadryl) and 250 mg of methylprednisolone (Solu-Medrol).

The autologous bone marrow was infused 48 hr after the last dose of chemotherapy. One patient, patient 9 in Table 2, died too early to receive his transplant, and for patient 4 in Table 3, the first course consisted of a lower dose of CV without transplant.

Most patients who received a second course of therapy were given marrow obtained before the initial course. However, in patients 7 and 10, bone marrow was collected after recovery from the first course and was reinfused after the second therapy (see also Table 7).

## RESULTS

*Therapeutic response*

The individual responses and response duration are given in Table 3. Of the 13 patients, 3 were inevaluable because of early deaths. In the 10 evaluable patients, there were 4 complete responders, 3 partial responders, 2 less than partial responders and 1 non-responder. Complete remissions occured in one patient treated with CV, two with CBV and one with CV-platinum. The median duration of CR was 15.5 weeks and the median duration of response 15 weeks (excluding less than partial). Of the 4 complete responders, 2 (patients 7 and 10) relapsed before receiving further chemotherapy; the other 2 were maintained on adriamycin–bleomycin (patient 4) and low dose CV-platinum (patient 13) and eventually relapsed on these regimens. Of the 3 patients with PR, two relapsed before receiving further chemotherapy. Patient 6, whose measurable disease consisted of minimal retroperitoneal lymphadenopathy, had an elevated beta human chorionic gonadotropin ($\beta$-HCG) level of 8234 I$\mu$/ml ($N = <3$) and an alpha fetal protein level of 23.7 ng/ml ($N = <15$), had a disappearance of intravenous pyelogram abnormalities and reduction in marker levels to 5.1 I$\mu$/ml and 3.8 ng/ml, respectively. He subsequently received a third course of CV followed by autologous transplantation of marrow collected after the second course without further reduction in marker levels.

The median survial of all patients was 10 weeks; 19 weeks for the ten evaluable patients and 20 weeks for the seven responding patients. Four possibly treatment related deaths are summarized in Table 4. With regard to these patients, the following comments are made: (i) the only two patients with fever before commencement of high dose chemotherapy are included in this group; (ii) three of the four patients were heavily pretreated for periods of 9–12 months with five or more drugs including alkylating agents, actinomycin D, vinblastine and platinum; (iii) all four patients died of infectious complications, with evidence of fungal infection occurring in three of the four; and (iv) three of the four patients had more than 1500 granulocytes/mm$^3$ for at least 6 days before death.

These data suggest that immunosuppression more than neutropenia played an important role in these treatment-related deaths. Prior extensive chemotherapy probably contributed substantially to this immunosuppression.

*Non-hematological toxicity*

The incidence of non-hematological toxicities after administration of high dose CV or CBV is summarized in Table 5. Gastrointestinal toxicities included nausea, vomiting, stomatitis and diarrhea. Only in the

*Table 4. Treatment-related deaths*

| Patient number | Cause of death | Myelosuppressed at time of death | Time of death after chemotherapy (days) | Fever before high dose chemotherapy |
|---|---|---|---|---|
| 1 | Disseminated candidiasis | No | 26 | No |
| 7 | Gram-negative septicemia | No | 120 | No |
| 8 | Pulmonary infiltrates yeast and gram negative organisms in sputum | Yes | 18 | Yes |
| 11 | Candida and gram-negative septicemia | No | 35 | Yes |

*Table 5. Non-hematological toxicity of megadose chemotherapy*

| Toxicity | Incidence | |
|---|---|---|
| | CV (9 courses) | CBV (5 courses) |
| Gastrointestinal | | |
| Stomatitis | — | — |
| able to eat | 1 | 2 |
| unable to eat | 1 | 1 |
| Nausea and vomiting | | |
| mild (<2/day) | 2 | 2 |
| moderate (<6/day) | 5 | 3 |
| severe (>6/day) | 2 | — |
| Diarrhea | 2 | 1 |
| Hepatic | | |
| Transaminase <60 Mμ/ml | — | 2 |
| Transaminase >60 Mμ/ml | — | 1 |
| Hemorrhagic cystitis | — | 1 |
| Mental changes | 1 | 1 |
| Myalgia | 4 | — |

CV = cyclophosphamide and VP-16.
CBV = cyclophosphamide, BCNU and VP-16.

one patient receiving CV-platinum (not included in the table) was vomiting so severe that the fourth day of proposed chemotherapy had to be deleted. The episode of hemorrhagic cystitis occurred in patient 7, the one who received cyclophosphamide as a single infusion; no cystitis was seen after dividing the cyclophosphamide in daily doses over 3–4 days. Several patients experienced episodes of generalized muscle pains without evidence on physical examination of myositis or motor disturbances. In at least one patient, pains coincided with administration.

*Hematological toxicity*

Details on the duration of and recovery from hematopoietic suppression calculated from the first day of CV or CBV chemotherapy are given in Table 6. All patients experienced rapid myelosuppression; neutrophils were less than $0.5 \times 10^9$/liter by a median of 9 days and platelets less than $50 \times 10^9$/liter by day 13. The patients in the CV group were neutropenic and thrombocytopenic for approximately 2 weeks; these levels recovered approximately 3 weeks after chemotherapy, day 16 after autologous bone marrow transplantation. Platelet levels did not recover in one patient until day 42+; however, his marrow was collected and chemotherapy commenced when the platelet count was only $80 \times 10^9$/liter.

The recovery in CBV patients can be compared to that obtained in a larger series of patients, most of them with the diagnosis of small cell carcinoma of the lung, described earlier [8]. Recovery to more than $1.5 \times 10^9$/liter granulocytes in three evaluable courses was 28 days, similar to that reported in reference [8].

Three patients in the CV group and two treated with CBV received a second course, the former three with marrow collected before the initial chemotherapy, the latter two with marrow collected after the first course. As can be seen in Table 7, the degree of myelosuppression is the same in both courses for the CV group, whereas the CBV patients experienced clearly prolonged myelosuppression compared to the first one. However, it must be remembered that the marrow used for transfusion after the second course of CBV was collected after the first high dose therapy.

*Table 6. Hematological recovery after high dose chemotherapy with ABMT (first course)*

| | | CV (11 courses) | | | | CBV (3 courses) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Duration in days | | Recovery | | Duration in days | | Recovery | |
| | | Median | Range | Median | Range | Median | Range | Median | Range |
| Granulocytes | $<500$ | 11 | 9–28 | 19 | 15–35 | 12 | 8–25 | 21 | 18–33 |
| | $<1000$ | 12 | 10–28 | 21 | 18–35 | 21 | 12–26 | 28 | 22–33 |
| | $<1500$ | 14 | 11–28 | 23 | 18–35 | 24 | 21–26 | 28 | 23–33 |
| WBC | $<1000$ | 10 | 7–26 | 19 | 15–35 | 14 | 8–17 | 21 | 21–29 |
| Platelets | $<20$ | 2 | 0–34 | 16 | 16–42 | 10 | 7–19 | 21 | 18–24 |
| | $<50$ | 7 | 2–34+ | 20 | 15–42+ | 16 | 11–22 | 27 | 23–31 |
| | $<100$ | 10 | 5–34+ | 21 | 16–42+ | 21 | 14–25 | 30 | 24–35 |

Four courses of CV did not reduce platelets to less than $20 \times 10^9$/liter.
One patient with CV started with $80 \times 10^9$/liter platelets and had not recovered to more than 50 $\times 10^9$/liter at day 42. These figures are calculated from the first day of chemotherapy and not the day of transplantation. To determine recoveries from the day of transplantation usually subtract 5 days.

*Table 7. Hematological toxicity of second courses of CBV or CV*

| | | CV (3 patients) | | | | CBV (2 patients) | |
|---|---|---|---|---|---|---|---|
| | | Course 1 | | Course 2 | | | |
| | | Median | Range | Median | Range | Course 1 | Course 2 |
| Granulocytes | $<500$ | 17 | 15–18 | 19 | 19–21 | 18 : 21 | 34 : 36+ |
| | $<1000$ | 19 | 18–21 | 21 | 20–22 | 22 : 28 | 40 : 36+ |
| | $<1500$ | 20 | 18–23 | 24 | 23–25 | 23 : 28 | 41 : 36+ |
| WBC | $<1000$ | 16 | 15–18 | 19 | 18–21 | 18 : 21 | 34 : 27 |
| Platelets | $<20$ | — | — | 16 | 16–18 | 21 : 21 | 42 : 30 |
| | $<50$ | 17 | 15–18 | 17 | 16–21 | 23 : 27 | 43 : 36+ |
| | $<100$ | 18 | 18–21 | 20 | 19–23 | 24 : 30 | 47 : 36+ |

CV patient's bone marrow was collected before course No. 1 and was transplanted after course Nos. 1 and 2. CBV patient's bone marrow was collected before course No. 1 and was transplanted after course No. 1; bone marrow collected before course No. 2 was transplanted after course No. 2. These figures are calculated from the first day of chemotherapy and not the day of transplantation. To determine recoveries from the day of transplantation usually subtract 5 days.

In only one patient given CV were WBC transfusions given; the majority of patients received two or more units of platelets and red blood cells.

*Infectious complications*

Infectious complications contributed most to treatment-related morbidity and mortality and no major bleeding episodes secondary to thrombocytopenia were encountered. Table 8 summarizes the number of febrile days, as well as the number of episodes of bacterial and fungal infections, seen in 11 courses of CV. As noted earlier, the two patients with candida septicemia died from this complication. Three of eleven courses were not complicated by fever at all. Most febrile episodes responded rapidly to treatment with antibiotics alone. In eleven courses of CV, prophylactic antibiotics were given in six: in three out of these six, no fever occurred, as opposed to its occurrence in five of five courses not treated prophylactically.

All patients treated with CBV (6 courses) experienced fever (mean of 12 days) of which two remained unexplained. Four episodes of bacterial and two episodes of fungal infection occurred; the two patients with fungal infections (one in sputum, one in esophagus) are included in the treatment-related deaths.

## DISCUSSION

We report here on the effects of treating refractory nonseminomatous germ cell tumors

*Table 8. Infectious complications after high dose CV*

| | Incidence (11 courses) | Type |
|---|---|---|
| Febrile days, Mean (range) | 8 (0–22) | — |
| Courses without fever | 3 | — |
| Fever of unknown origin | 4 | — |
| Bacterial infections | 2 | *Staph. aureus* cellulitis<br>Gram negative septicemia |
| Fungal infections | 4 | 2 candida stomatitis<br>2 disseminated candidiasis |
| Unknown | 1 | Bilateral pneumonia of unknown origin |

This includes the patients treated with CV-adriamycin and CV-platinum.

with higher than conventional doses of cytotoxic drugs. Animal studies have shown the relation between the dose of active drugs given and the degree of tumor kill obtained. In human systems, the most convincing data showing this relation are the increased number of long term survivors after treatment of relapsed leukemic patients with total body irradiation, cyclophosphamide and transplantation of identical twin marrow [15] and the higher complete remission rates in small cell bronchogenic carcinoma [16] or Burkitt's lymphoma [10] after treatment with escalated chemotherapy doses. Obviously, bleomycin and platinum, active drugs in testicular carcinoma, have primarily dose-limiting side effects other than myelosuppression, and therefore are not candidates for dose escalation. On the other hand, cyclophosphamide has been used extensively in high doses for the treatment of relapsed leukemia and lymphoma [10, 14] and has been shown to be effective in testicular carcinoma [11]. Preliminary evidence showed VP-16 to be active in testicular carcinoma [8, 12]. Experience with the administration of high doses of this drug was previously obtained in our institution in the treatment of acute lymphatic leukemia in remission and small cell carcinoma of the lung. The combination of cyclophosphamide-VP-16, which moreover might be synergistic [17], was the backbone of the program described here.

The possible comparable second-line study in Table 9 is that of Williams and Einhorn [12]. It is the only reported study on patients failing platinum-containing programs. Indeed, VP-16-213 in combination with platinum would appear at least as active as the study reported here; producing an almost 100% response rate and a 38% CR rate. However, the patient population must have contained a considerable portion of initial complete responders as 82% of Einhorn's patients were rendered free of disease by initial vinblastine–bleomycin–platinum therapy [2, 3]. However, only one of our patients had a CR to platinum or platinum-containing programs, a good reflection of the chemotherapy resistance of this group of patients. The non-comparability of this group of patients with other studies made it impossible to assess the true activity of this program, particularly whether any increased therapeutic effect was obtained through escalated drug doses.

The program clearly has not been able to induce durable complete remissions. In this respect, it appears to be comparable to most other second line treatments, which notoriously have not been very successful.

The non-myelosuppression toxicity of the program was mild, and consisted mainly of nausea and vomiting. It is therefore probable that further dose escalation would be feasible in better performance status patients.

Infectious complications were responsible for the four treatment-related deaths as well as for almost all nonlethal morbidity. The treatment-related deaths were in majority in part related to the extensive pretreatment. Moreover, fulminant fungal infection remains an important problem even in patients with good performance status who were only pretreated moderately, as evidenced by one patient. On the other hand, the majority of courses, despite the potentially lethal doses of VP-16 and cyclophosphamide, were complicated only by fever without proven infection which responded rapidly to the usual antibiotic coverage.

The aim of this study was not to determine whether autologous bone marrow transplantation hastened hematopoietic recovery after high dose chemotherapy. In the CV program.

*Table 9. Embryonal cell carcinoma: response to secondary therapy*

| Investigator | No. of patients | Therapy | Prior therapy | Response (%) CR | PR | NR | Response duration (months) CR | CR+PR |
|---|---|---|---|---|---|---|---|---|
| Klep [4] | 12 | VCR, A, CTX, Ad Progesterone (VACAM) | ? | 3 (25) | 5 (42) | 4 (33) | — | — |
| Klepp [4] | 19 | VCR, AD, MTX, B | VACAM | 0 | 1 (15) | 18 (95) | — | 4* |
| Klepp [4] | 5 | VCR, B, Mit | VACAM | 0 | 0 | 1 (100) | — | — |
| Kardinal [5] | 20 | V, B, A | ? | — | 2 (10) | 18 (90) | — | — |
| Burgess [6] | 14 | VCR, A, B | AD-5,† V-1, Mit-1 Others-6 | 5 (36) | 6 (43) | 3 (21) | | |
| Reynolds [18] | 19 | Vindesine | ? | 3 (16) | 16 (84) | — | — | 3* |
| Einhorn [3] | 10 | P, B, V | ? | 7 (70) | — | — | — | — |
| Cheng [19] | 25 | V, AD, B, P (VAB-II) | ? | 10 (40) | 3 (32) | — | 8† | — |
| Cvitokovic [20] | 16 | VAB-II | VB, AD | — | 11 (69) | — | — | 2–7+ |
| Einhorn [7] | 10 | A, P | VB-10, AD-5, Mit-2, CTX-2 VCR-1 | 1 (10) | 9 (90) | — | — | 5* |
| Williams [12] | 2 | VP-16 | Multiple | — | 2 (100) | — | — | — |
| Williams [12] | 16 | VP-16, P, A, B | P, V, B | 4 (25) | 12 (75) | — | 2+, 4+, 6+, 11+ | — |
| Williams [12] | 6 | VP-16, P, +/-B | P, V, B | 2 (33) | 3 (50) | — | 8+, 11+ | |

V, Vinblastine; B, bleomycin; P, *cis*-platinum (CDDP); AD, actinomycin D; A, adriamycin; VCR, vincristine; CTX, cyclophosphamide; MTX, mitomycin; Mit, mithramycin; CR, complete remission; PR, partial response; NR, no response.
*Median.
†Number of patients.

the median duration of granulocytopenia ($<1500/mm^3$) was 14 days with recovery at day 23, similar to that of thrombocytopenia. These recovery times are comparable to or even slightly better than those obtained in relapsed leukemia patients [14], patients with small cell carcinoma of the lung [8] or patients with malignant lymphoma [10]. Evidence in favor of at least some beneficial effect of the autologous transplant has been discussed elsewhere [8, 9, 21]. In view of the potential dangers of prolonged myelosuppression in heavily pretreated, frequently poor performance status patient groups, we were reluctant to test the hypothesis that the period of significant neutropenia and thrombocytopenia after $4.5\,g/m^2$ cyclophosphamide and $600\,mg/m^2$ VP-16 without autologous marrow rescue is approximately 2 weeks, as in this study.

We feel that the experience obtained justifies further development of this program. Such a program may be of further therapeutic benefit for Stage III nonseminomatous testicular carcinoma patients initially treated with vinblastine–bleomycin–platinum who achieve only a partial response. This program may also be useful for intensification of those Stage III patients with bulky pulmonary disease, a subgroup known to have a long term bad prognosis. These groups of patients would, because of less prior debilitating chemotherapy, experience less morbidity or mortality.

## REFERENCES

1. M. L. Samuels, D. E. Johnson and P. Y. Holye, Continuous intravenous bleomycin (NSC-125066) therapy with vinblastine (NSC-49842) in Stage III testicular neoplasia. *Cancer Chemother. Rep.* **59,** 563 (1975).
2. L. H. Einhorn and J. Donohue, *Cis*-diamminedichloroplatinum, vinblastine and bleomycin combination chemotherapy in disseminated testicular cancer. *Ann. int. Med.* **87,** 293 (1977).
3. L. H. Einhorn, Combination chemotherapy with *cis*-dichlorodiammineplatinum (II) in disseminated testicular cancer. *Cancer Treat. Rep.* **63,** 659 (1979).

4. O. KLEPP, R. KLEPP, H. HOST, G. ASBJØRNSEN, K. TALLE and E. STENWIG, Combination chemotherapy of germ cell tumor of the testes with vincristine, adriamycin, cyclophosphamide, actinomycin D and medroxyprogesterone acetate. *Cancer (Philad.)* **40,** 638 (1977).
5. C. G. KARDINAL, E. M. JACOBS, F. BULL, J. R. BATEMAN and T. PAJAK, Evaluation of bleomycin, adriamycin and vinblastine in combination therapy for advanced testicular tumors. *Cancer Treat. Rep.* **60,** 953 (1976).
6. M. A. BURGESS, L. H. EINHORN and J. A. GOTTLIEB, Treatment of metastatic germ-cell tumors in men with adriamycin, vincristine and bleomycin. *Cancer Treat. Rep.* **61,** 1447 (1977).
7. L. H. EINHORN and S. D. WILLIAMS, Combination chemotherapy with *cis*-dichlorodiammineplatinum (II) and adriamycin for testicular cancer refractory to vinblastine plus bleomycin. *Cancer Treat. Rep.* **62,** 1351 (1978).
8. G. SPITZER, K. A. DICKE, J. LITAM, D. S. VERMA, A. ZANDER, V. LANZOTTI, M. VALDIVIESO, K. B. MCCREDIE and M. L. SAMUELS, High dose combination chemotherapy with autologous bone marrow transplantation in adult solid tumors. *Cancer (Philad.)* **45,** 3075 (1980).
9. G. SPITZER, K. A. DICKE, D. S. VERMA, A. ZANDER, J. LITAM, A. DISTEFANO and V. LANZOTTI, High dose chemotherapy with autologous bone marrow transplantation. *Exp. Hematol.* **7,** (Suppl. 5), 38 (1979).
10. F. R. APPELBAUM, A. B. DEISSEROTH, R. G. GRAW, Jr., G. P. HERZIG, A. S. LEVINE, I. T. MAGRATH, P. A. PIZZO, D. G. POPLACK and J. L. ZIEGLER, Prolonged complete remission following high dose chemotherapy of Burkitt's lymphoma in relapse. *Cancer (Philad.)* **41,** 1059 (1978).
11. C. D. BUCKNER, R. A. CLIFT, A. FEFER, D. D. FUNK, H. GLUCKSBERG, P. E. NEIMAN, A. PAULSEN, R. STORB and E. D. THOMAS, High dose cyclophosphamide (NSC-26271) for the treatment of metastatic testicular neoplasms. *Cancer Chemother. Rep.* **58,** 709 (1974).
12. S. D. WILLIAMS, L. H. EINHORN, A. GRECO, R. OLDHAM, R. FLETCHER and W. H. BOND, VP-16-213: an active drug in germinal neoplasms. *Proc. Amer. Ass. Cancer Res.* **20,** 72 (1979) (Abstract No. 291).
13. J. G. MAIER and M. H. SULAK, Radiation therapy in malignant testis tumors. *Cancer (Philad.)* **32,** 1212 (1973).
14. K. A. DICKIE, A. ZANDER, G. SPITZER, D. S. VERMA, L. PETERS, L. VELLEKOOP and K. B. MCCREDIE, Autologous bone marrow transplantation in adult leukemia in relapse. *Lancet* **i,** 514 (1979).
15. A. FEFER, C. D. BUCKNER, E. D. THOMAS, M. A. CHEEVER, R. A. CLIFT, H. GLUCKSBERG, P. NEIMAN and R. STORB, Cure of hematologic neoplasia with transplantation of marrow from identical twins. *New Engl. J. Med.* **297,** 146 (1977).
16. P. A. BUNN, Jr., M. H. COHEN, D. C. IHDE, B. E. FOSSIECK, Jr., M. J. MATTHEWS and J. D. MINNA, Advances in small cell bronchogenic carcinoma. *Cancer Treat. Rep.* **61,** 333 (1977).
17. P. DOMBERNOWSKY and N. I. NISSON, Combination chemotherapy with VP-16-213 in L1210 leukemia. *Proc. Amer. Ass. Cancer Res.* **16,** 167 (1975).
18. T. F. REYNOLDS, D. VUGRIN, E. CVITKOVIC, R. J. GRALLA, C. W. YOUNG and R. B. GOLBEY, Phase II trail of vindesine in patients with germ cell tumors. *Cancer Treat. Rep.* **63,** 1339 (1979).
19. E. CHENG, E. CVITKOVIC, R. E. WITTES and R. B. GOLBEY, Germ cell tumors: VAB II in metastatic testicular cancer. *Cancer (Philad.)* **42,** 2162 (1978).
20. E. CVITKOVIC, V. CURRIE, I. H. KRAKOFF and R. GOLBEY, Bleomycin infusion with *cis*-platinum diammine dichloride as secondary chemotherapy for germinal cell tumors. *Proc. Amer. Ass. Cancer Res.* **16,** 273 (1975).
21. F. R. APPELBAUM, G. P. HERZIG, J. L. ZIEGLER, A. S. LEVINE and A. B. DEISSEROTH, Successful engraftment of cryopreserved autologous bone marrow in patients with malignant lymphomas. *Blood* **52,** 85 (1978).