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VP16-213, Cisplatinum, and Adriamycin Salvage Therapy of Refractory and/or Recurrent Nonseminomatous Germ Cell Neoplasms*

J. Mortimer[1], R. M. Bukowski[1], J. Montie[2], J. S. Hewlett[1], and R. B. Livingston[1]

[1] Department of Hematology and Medical Oncology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44106

[2] Department of Urology, Cleveland Clinic, Cleveland, Ohio 44106, USA

Summary. *Eleven patients with recurrent and/or resistant nonseminomatous germinal cell neoplasms refractory to conventional chemotherapy were treated with the combination VP16-213, cis-diamminedichloroplatinum, and adriamycin. One complete response, four partial responses which at surgery were benign teratomas, and six partial responses have been observed. Four patients are prolonged survivors (> 18 months). The possibility that this regimen may offer true salvage for refractory patients exists. Incorporation of VP16-213 into initial treatment regimens for germinal cell neoplasms is warranted.*

Introduction

Major advances have taken place in the treatment of testicular cancer. In the 1960's approximately 45% of patients treated with chemotherapy for disseminated disease responded objectively and 15% attained a complete remission. Of these, only one-half were long-term disease-free survivors. With present therapy, the projected cure rate for metastatic nonseminomatous germ cell cancer now approaches 70% [2]. A small but significant percentage of patients fail to achieve durable responses to first line therapy. In an effort to retrieve these patients, a number of single agents and combinations have been tried with varying success. The investigational epipodophyllotoxin VP16-213 has been evaluated in a variety of hematologic and solid tumors [3]. Its major dose-limiting toxicity is myelosuppression, which is modest, and it thus appears suitable for combination chemotherapy. Additionally, in view of its mechanism of action which appears to be the induction of a pre-mitotic block [5], it theoretically may be synergistic with bleomycin. Also, in vivo, therapeutic synergy with cisplatin (DDP) has been demonstrated in P388 cancer-bearing mice (Issell B, personal communication).

Phase II information with VP16-213 is available for 61 patients with germinal cell tumors who had failed previous therapy [1, 4, 7]. Nineteen of 56 evaluable patients demonstrated responses in these reports. In view of this information, VP16-213 has been combined with adriamycin and DDP as second-line therapy for treatment of patients with nonseminomatous neoplasms who have failed to achieve a complete response or show progressive disease with initial therapy [8]. The purpose of this paper is to report our experience with this salvage regimen.

Patients and Methods

Between January 1980 and June 1981, 11 patients have received chemotherapy with VP16-213, adriamycin and cis-platinum. Patients were considered eligible for this study if they either were unresponsive to conventional chemotherapy, e.g., Velban, DDP, and bleomycin (VBP), relapsed following adjuvant therapy, or had relapsed following conventional chemotherapy. Histologically, only patients with nonseminomatous tumors were eligible, and both patients with gonadal and extragonadal primary sites were acceptable. All patients had measurable disease in the form of easily defined tumor masses.

Chemotherapy consisted of the following: adriamycin 50 mg/m^2 i.v. d1, VP16-213 90 mg/m^2 i.v. d1–5, DDP 20 mg/m^2 i.v. d1–5. Courses were repeated at 4-week intervals if toxicity allowed. During DDP therapy patients were hydrated with 1,000 cc of normal saline, and received 12.5 mg of mannitol 1 h prior to its administration. Prior to each course of therapy, a complete physical examination was performed, and the size of all measurable lesions determined. A complete blood count with platelets was obtained before each treatment, and on day 14 of each course. Prior to each course of therapy, the following biochemical studies were obtained: BUN, creatinine, SGOT, SGPT, alkaline phosphatase, bilirubin, urinalysis, LDH, β-subunit HCG, alpha-feto protein (AFP). Audiograms and electrocardio-

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grams were obtained pretreatment, and repeated if initially abnormal or clinically indicated.

In patients who were partial responders or demonstrated stable disease following four courses of chemotherapy, complete clinical restaging (computerized tomography of abdomen and chest, β-subunit HCG, LDH, and AFP) was obtained, and if possible all residual disease was surgically removed. All patients demonstrating progressive disease were removed from the study. In complete responders, or in patients with no disease following surgery, maintenance therapy was given, but the type was variable and up to the individual physician.

A complete remission (CR) was defined as complete disappearance of all evident disease for at least 2 months. A partial remission was defined as more than a 50% reduction of the sum of the product of the perpendicular diameters of all measurable lesions and of any previously abnormal tumor markers for at least 2 months. Stable disease was minor regression or no change in size of all measurable lesions, with no increase in tumor markers compared to pretreatment values. Progressive disease was an increase of 25% or greater of any measurable lesion.

Table 1 summarizes data on the three patients who received adjuvant therapy for stage II testicular carcinoma, subsequently relapsed, and then were placed on salvage therapy. Table 2 summarizes the data on eight patients who presented with metastatic disease, and subsequently progressed or did not respond to initial therapy and were then treated with the VP16 containing combination. Median survival times were estimated employing Kaplan-Meier survival curves.

Results

Eleven of 11 patients responded to salvage chemotherapy. One CR and 10 PR's occurred. A median of four courses of chemotherapy was given (range 1–4). The projected median survival from the initiation of salvage chemotherapy is 12.5 months, and from the time of initial diagnosis 23.5 months.

Table 1. Characteristics of patients receiving previous adjuvant therapy

Patient	Age	Cell type	Previous therapy	Disease free interval	Response	Survival[b] (mos.)
1	23	Embryonal + choriocarcinoma	DDP, bleomycin, VCR, Actinomycin D	7.0	PR	9.0+
2	17	Embryonal + choriocarcinoma	VB,[a] × XRT	21.0	PR, NED with surgery	12.0+
3	24	Mixed	VB, XRT	11.0	CR	12.0

[a] VB: velban, bleomycin
[b] From start VP16-213, adriamycin, DDP

Table 2. Characteristics of patients previously treated for metastatic disease

Patient	Age	Cell type	Previous therapy	Response	Overall survival (mos.)	Survival from start salvage regimen (mos.)
4	23	Embryonal	VBP[b]	PR	33.0 +	9.0 +
5[a]	40	Embryonal + Terato Ca	FAC[c]	PR	12.0	12.0
6	27	Embryonal	VBP	PR, NED with surgery	26.0 +	21.0 +
7	22	Embryonal + Seminoma	VBP	PR	18.0	9.0
8	20	Chorio Ca + Terato	VBP	PR, NED with surgery	18.0 +	15.0 +
9[a]	25	Terato Ca	VBP	PR, NED with surgery	34.0 +	27.0 +
10	24	Mixed	VBP	PR	23.0	7.0
11	24	Chorio Ca + Embryonal	VBP	PR	6.0 +	2.0 +

[a] Extragonal neoplasms
[b] VBP: vinblastine, bleomycin, DDP
[c] FAC: 5-Fluorouracil, adriamycin, cyclophosphamide

In the group receiving prior adjuvant therapy for stage II disease, three of three patients responded. One complete response was seen and consisted of normalization of a chest x-ray. This patient subsequently relapsed in the central nervous system (brain and spinal cord).

Eight patients were treated for metastatic disease initially. Responses to initial chemotherapy were as follows: one complete responder (normalization of a chest x-ray), five partial responders, two nonresponders. Seven of these patients received the combination of vinblastine, DDP, and bleomycin (VBP). A median of four courses was given (range 3–5), and the dosage of DDP in six of seven patients was 100 mg/m^2 per course, with it being unknown in the remaining patient. The eighth patient was diagnosed initially as metastatic carcinoma of unknown primary site and treated with 5-FU, adriamycin, and cyclophosphamide. All of these patients when placed on the salvage regimen demonstrated partial responses. Three of these patients were felt to be surgical candidates, and underwent excision of benign teratomas, and are alive 15–28 months from diagnosis. One patient is continuing therapy at present, and the remaining four have developed progressive disease.

Of special interest are the group of four patients (nos. 1, 6, 8, 9) who progressed while receiving a DDP containing combination. All four had partial responses to salvage chemotherapy, with two remaining disease-free at 25 and 28 months after resection of benign teratomas.

All the patients receiving VP16-213, adriamycin and DDP were heavily pretreated, and in view of this, the toxicity of the salvage regimen was substantial. All patients had severe nausea and vomiting, and developed alopecia. Severe mucositis was seen in five of 11 patients. Myelosuppression (leukocytes $\leq$ 3,000 cells/mm^3 and/or platelets $\leq$ 100,000/mm^3) occurred in all patients, and in four instances was life-threatening (leukocytes $\leq$ 1,000 cells/mm^3). These latter patients required hospitalization for antibiotics. No drug-related deaths occurred in the group, however.

Finally, maintenance therapy was given to three patients (nos. 2, 6, 9). This consisted of VP16-213 and adriamycin (one patient) and chlorambucil (two patients).

Discussion

The results of this study substantiate the efficacy of VP16-213 containing combination chemotherapy in the treatment of nonseminomatous germ cell neoplasms reported previously by Williams, et al. [8]. This regimen (VP16-213, adriamycin, and DDP) appears to offer the possibility of long-term survival even in patients failing first-line chemotherapy. In view of the long-term disease-free survival ($\geq$ 18 months) in several of our patients, true salvage and possibly cure may be reasonably expected.

Interestingly, the combination of VP16-213, adriamycin and cis-platinum was effective not only in patients who had not received prior cis-platinum, but even in a subset of patients who progressed while receiving a DDP combination. Two of these four have been rendered free of disease following surgery. Patients with extragonadal primary tumors have long been recognized as a poor prognosis group. Both of our patients with extragonadal tumors responded to salvage therapy. One is alive without evidence of disease after resection of benign teratoma 28 months from initial diagnosis.

The efficacy of this VP16-213 regimen indicates that it may have a possible role as first-line chemotherapy not only in patients with extragonadal germ cell neoplasms, but also in the group with testicular primaries and poor prognostic features [7] ($\geq$ 5 pulmonary metastases measuring $>$ 2 cm, palpable retroperitoneal mass, β-subunit HCG $\geq$ 1,000 units). Incorporation of VP16-213 into the VBP combination, replacement of vinblastine by VP16-213 in the VBP regimen, or alternating VBP and VP16-213, adriamycin, DDP, and bleomycin are three possible strategies for this approach. At the Cleveland Clinic, we are presently employing this last strategy in patients with extragonadal tumors, and testicular tumors having poor prognostic features. Six patients have been treated, and three are presently evaluable. Partial responses have been seen in three of three evaluable patients to date. Further investigation of VP16-213 in metastatic testicular cancer is necessary.

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