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VP 16 plus ifosfamide plus cisplatin as salvage therapy in refractory testicular cancer*

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Summary. In patients with refractory germ cell tumour who fail to achieve complete remission (CR) or which achieve CR but subsequently experience disease progression within 2 months of receiving cisplatin + vinblastine + bleomycin (PVB) the results of further treatment are poor. Similarly, third-line therapy after cisplatin with VP 16 salvage rarely produces clinically significant remission. From February 1983 to October 1984 we treated 53 patients with ifosfamide (1.2 g/m^2 per day on days 1–5), VP 16 (75 mg/m^2 per day on days 1–5), cisplatin (20 mg/m^2 per day on days 1–5), and *N*-acetylcysteine (2.0 g p.o. every 6 h on days 1–7). This was repeated every 21 days for four to six cycles. One group of patients (group A, 20 pts) had achieved partial remission (PR) but still had nonresectable tumours after PVB therapy; a further group (group B, 4 pts) had achieved CR with PVB but then experienced disease progression within 2 months; the remaining patients (group C, 28 pts) had experienced disease progression after one or more salvage attempts, including therapy with cisplatin and VP 16. Of the original 53 patients, 51 were evaluable for response. Toxicity included moderate to severe myelosuppression in almost all patients, fever/sepsis in 8, creatinine $\geq$ 6 mg% in 4, and hematuria in 4 patients. There were no drug-related deaths. CR was attained in 17/51 patients (34%), these being 8/20 in group A, 1/4 in group B, and 8/28 in group C, and 10 patients have remained in CR for periods ranging from over 1 month to over 17 months. PR was achieved in 20 patients (40%), but their median duration of remission was only 2 months. We feel these results, obtained in a poor-prognosis patient population, are sufficiently encouraging to warrant further study of this regimen, including investigation of its use as initial salvage therapy following PVB.

Introduction

Cisplatin-based combination regimens can be expected to produce complete remissions (CRs) in 70%–80% of treated patients with disseminated testicular cancer [12, 32]. Although these results are excellent, they still leave 20%–30% of patients who are candidates for salvage chemotherapy. VP 16, an epipodophyllotoxin, is one of the few agents that have been found to have single-agent activity in cisplatin-refractory patients [9, 13, 34]. Indeed, cisplatin plus VP 16 salvage chemotherapy has achieved durable CR in 25% of previously treated patients [15, 19, 21, 31, 34].

Ifosfamide, an oxazaphosphorine, is an analogue of cyclophosphamide, which differs from its parent compound in that myelosuppression is less common and hemorrhagic cystitis is the dose-limiting side-effect [6, 11]. With the development of effective uroepithelial protective agents (*N*-acetylcysteine or mesna) hemorrhagic cystitis has become easier to manage [7, 8, 20, 26]. Several European investigators have reported single-agent activity for ifosfamide in refractory testicular cancer. In 18 patients with advanced testicular cancer (11 previously treated) 15 patients responded, including 2 with complete and 13 with partial remissions. The median remission time was 5.4 months, and the median survival time of the responders was 11 months [29]. Similar responses have been reported by other workers [4, 18, 27]. Interpretation of these studies has been difficult, as prior dosages and scheduling of chemotherapy and previous response were not readily accessible. In addition, it was uncertain how many patients were truly refractory to induction chemotherapy (i.e., progressing within 3 weeks of the latest course of therapy) and not experiencing late relapses after CR.

On the basis of the published results, we embarked on a phase II trial to investigate the single-agent activity of ifosfamide in patients with germ cell tumors refractory to cisplatin [33]. We treated 30 patients with advanced refractory disease with ifosfamide (2 g/m^2 per day) for 5 consecutive days every 3 weeks. Partial remission (PR) was achieved in six patients and complete remissions (CR) in one (overall response rate 23%). The median duration of response was 3.5 months with a median survival time for all patients of 3.5 months. Unfortunately, like single-agent VP 16, ifosfamide failed to produce durable remissions in these refractory patients. We found this activity impressive nonetheless, as in our experience VP 16 has been the only single agent to demonstrate activity in patients refractory to cisplatin.

As a result of this single-agent activity and known preclinical synergy of oxazaphosphorines plus cisplatin [4, 25, 26], we embarked on a trial of cisplatin and ifosfamide, plus VP 16 as salvage therapy for patients with refractory germ cell tumors.

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Table 1. Modified M. D. Anderson staging system

A.	Minimal pulmonary disease
B.	Advanced pulmonary disease
C.	Minimal abdominal with or without pulmonary disease
D.	Advanced abdominal with or without pulmonary disease
E.	Serum marker only
F.	CNS, bone, extra-abdominal nodal, etc.

"Minimal" disease is defined as stage A, C or E; Advanced, as stage B, D or F

Materials and methods

From February 1983 through October 1984, 50 previously treated patients with advanced germ cell tumors were seen at Indiana university and treated with chemotherapy. All but one of these patients had previously received cisplatin, vinblastine, and bleomycin combination chemotherapy and failed to be cured; 41 had primary testicular cancer, while 9 had primary extragonadal germ cell tumors (retroperitoneum 2; mediastinum 7). Patients entered into this study had PR with tumor still not resectable ("unresectable partial remission") as a best response to PVB (group A), attained CR but relapsed within 2 months after completion of induction chemotherapy (group B), or also received cisplatin plus VP 16 as salvage therapy, and thus received cisplatin + VP 16 + ifosfamide as third-line chemotherapy (group C). Two patients were ineligible for evaluation (one patient with falsely elevated marker and one patient without measurable disease), leaving 48 evaluable patients. Using a modification of the M. D. Anderson Staging System (Table 1) 11 patients were classified as having minimal and 37 patients as having advanced disease. Patient characteristics are described in Table 2.

The VIP treatment regimen consisted in VP 16 (75 mg/m^2), ifosfamide (1.2 g/m^2), and cisplatin (20 mg/m^2), all given daily for 5 consecutive days. In addition, the uroepithelial protective agent *N*-acetylcysteine (NAC) was administered at a dosage of 2.0 g (four 500-mg capsules supplied by Mead-Johnson Pharmaceutical Company, Evansville, Ind) p.o. every 6 h, starting within 1 h before ifosfamide and continued until 36 after the last dose of ifosfamide. For patients with prior abdominal, pelvic, or chest radiotherapy the doses of both ifosfamide and VP 16 were reduced by 25%. Urinalysis was repeated daily, and if more than 10 red blood cells/high-power field were noted ifosfamide was withheld until the hematuria resolved, while the NAC was increased to the same dose every 4 h. If hematuria recurred upon treatment with ifosfamide then subsequent ifosfamide dosages were decreased by 25%.

Courses were repeated every 21 days for four cycles. Dosage modifications included a 25% reduction in both ifosfamide and VP 16 for patients who developed a granulocytopenic fever or thrombocytopenic bleeding. Patients who demonstrated a rise in serum creatinine to 2 mg/dl or over had chemotherapy delayed until the creatinine stabilized, and subsequent ifosfamide dosages were reduced by 25% for these patients.

Pretreatment evaluation consisted of physical examination, urinalysis, complete blood count, and checks of SMA-12, electrolytes, creatinine, B-subunit human chorionic gonadotropin (BHCG), and alphafetoprotein (AFP). Chest roentgenogram and computed tomography of the abdomen or chest were performed when appropriate for measurements. Chest roentgenogram and all blood tests including serum markers were repeated every 3 weeks. Computed tomography was repeated at 9 weeks or as indicated to document remission. When feasible, resection of residual disease was performed 4–6 weeks after the final course of therapy. If examination of the resected disease revealed carcinoma, two further courses of VIP were administered.

Complete remission (CR) was defined as no evidence of disease by physical examination, roentgenographic studies and serum markers for at least 1 month. A partial

Table 2. Patient characteristics

	Group A ($N = 22$)	Group B ($N = 7$)	Group C ($N = 19$)	Total (%)
Histology				
Embryonal carcinoma	6	1	6	13 (27)
Teratocarcinoma	6	3	7	16 (33)
Choriocarcinoma	2	0	1	3 (6)
Seminoma	1	1	0	2 (4)
Combination of above	7	2	5	14 (29)
Site of primary				
Testis	18	5	16	39 (81)
Mediastinum	3	2	2	7 (15)
Retroperitoneum	1	0	1	2 (4)
Stage (Defined in Table 1)				
Minimal	2	2	7	11 (23)
Advanced	20	5	12	37 (77)
Previous treatment				
2 previous regimens	2[a]	1	11	14 (29)
≥3 previous regimens	1[a]	0	8	9 (19)
Prior cyclophosphamide	2	0	4	6 (12.5)
Previous radiotherapy (excluding brain)	1	0	2	3 (6)

[a] Not containing VP 16

remission (PR) was defined as a reduction in the extent of disease by 50% or more using the above criteria, as measured by the sum of the products of perpendicular diameters of bidimensionally measurable lesions and including a 90% or greater reduction in the pretreatment level of BHCG or AFP. All patients entered who received at least 1 day of therapy were considered eligible for evaluation of response and survival.

Results

Clinical response

All patients. CR was achieved in 13 patients, including four patients who underwent resection of residual disease revealing necrosis or fibrosis. Additionally 1 patient underwent resection of teratoma and 2 patients underwent resection of carcinoma following VIP therapy [total CR + NED after surgery = 16/48 (33%)]. Of the 48 evaluable patients, 20 (95% confidence limits are 20% and 47%) (42%) achieved PR, while 12 (25%) failed to respond. The median duration of CR was 9 months (range 2–26+), as against a median duration of remission of only 2 months for PR. The median survival time for all evaluable patients was – months (range 0–28+ months). Results for each of the subgroups are detailed individually.

Disease-free status was achieved with VIP in 4/11 (36%) patients with minimal and 12/37 (32%) with massive disease. Of the 6 patients who had received previous treatment with regimens containing cyclophosphamide, 3 attained CR (2 CR, 1 NED carcinoma); 2 of these 3 had not achieved a previous CR.

Among 39 patients with primary testicular carcinoma, 14 (36%) responded favorably, as opposed to 2 of the 9 patients with primary extragonadal germ cell tumors (both with primary retroperitoneal tumors).

With reference to histology, favorable responses were observed in 100% (2/2) of patients with seminoma, 31% (4/13) of those which embryonal carcinoma, 33% (1/3) of those with choriocarcinoma, 19% (3/16) of those with teratocarcinoma, and 43% (6/14) of patients with other mixed or unclassifiable germ cell neoplasms.

Clinical response

Subgroups. In group A, 6/22 (27%) patients achieved CR (95% confidence limits are 9% and 46%). Details of these patients are outlined in Table 3. Of these 6 patients, 3 remain free of disease at 10, 23, and 26 months from the start of therapy.

In group B, 3 of the 7 patients attained a second CR with VIP, lasting 3, 5 and 9 months (Table 3).

In group C, 7/19 (37%) patients achieved CR (95% confidence limits are 17% and 58%). The median duration of remission for this group was 9 months (range 5–21 months). Three patients remain alive and in remission 9, 16, and 25 months (Table 3).

Toxicity

Nausea and vomiting occurred in virtually all patients, but was severe in only 10. Myelosuppression was severe, 75% of patients having white blood count (WBC) nadirs $\leqslant 1000/mm^2$ and 33% $\leqslant 500/mm^3$. Similarly, thrombocytopenia was also severe, 66% of the patients having platelet count nadirs $\leqslant 50000/mm^3$ and 26% $\leqslant 20000/mm^3$. The median WBC and platelet nadirs were $900/mm^3$ and $24000/mm^3$, respectively. There were 14 (26%) patients who developed granulocytopenic fever requiring hospitalization and i.v. antibiotics, and 3 patients had documented sepsis.

Nephrotoxicity (serum creatinine $\geqslant 2$ mg%) occurred in 7 (15%) patients, including 3 with creatinines $\geqslant 6$ mg%. None of these patients required dialysis. There were 7 (15%), patients who developed macroscopic hematuria, and 1 additional patient complained of dysuria without hematuria. Other side-effects included headaches in 2 patients, and congestive heart failure and hypokalemia, which each occurred in 1 patients. Only 4 otherwise responding patients received fewer than two courses of therapy because of gastrointestinal or urological side-effects. There were no drug-related deaths.

Discussion

Patients who are not cured with induction chemotherapy generally have a poor prognosis. Platinum/VP 16 combination regimens have nonetheless produced durable CR in approximately 25% of patients. For the remainder of these patients, unique forms of therapy are obviously indicated.

Predictive prognostic factors for salvage therapy in testicular cancer are difficult to elucidate, because of the small numbers of such patients. In our experience, however, failure to achieve CR or early relapse (within 2 months) from CR have only occassionally been followed by long-term survival with cisplatin + VP 16 salvage chemotherapy [35]. In support of this, Bosl et al. reported only two PRs and no CRs with cisplatin + etoposide in 14 patients with previously unresectable partial remission in response to induction chemotherapy [3]. In contrast, Hainsworth et al. reported 7 CRs among 23 (30%) patients when they used these same agents in patients who had previously been in unresectable PR [15]; 4 of these 7 patients treated at Indiana University, however, did demonstrate normalization of serum markers with induction chemotherapy but were left with persistent roentgenographic abnormalities before being found later to have progressive disease [2]. In our series, 16/22 patients defined as having unresectable PR had previously failed to normalize serum markers with induction chemotherapy.

Thus, the term unresectable PR' usefully defines a particular type of response. Prospectively, the response in patients who have roentgenographic plus concurrent serologic abnormalities clearly meets this definition. For those patients with residual radiographic disease and normal markers following induction chemotherapy, however, the term unresectable PR is not always appropriate. While some patients will later relapse with progressive cancer manifested by serum markers and/or roentgenographically, other patients may continue to show regression (implying necrotic tumor) or confined stability (implying teratoma). In the first group it is only when a patient develops progressive disease that he or she can be correctly (but retrospectively) known to have had residual cancer. In the last two situations, salvage chemotherapy would be unnecessary. Whether these subgroups of patients with unresectable PR have different prognoses remains uncertain. Thus, because of uncertainties in the historical data, it remains uncertain from this series whether or not ifosfamide adds to the

Table 3. Clinical data of complete responders to VIP

Patient	Pathology	Primary site	Prior therapy	Response to prior therapy	Metastatic sites	Dosage extent[f]	Response to VIP	Remission duration (months)	Survival (months)
Group A									
1	C	RP	PVB x 3	PR[e]	Lung, liver, BHCG, RPLN	D	CR	26+	19+
2	S/TER	T	POB x 4	PR	Liver, lung RPLN	D	CR	2	7
3	EC	T	PVB x 3	PR[e]	Lung RPLN	D	CR	7+	10+
4[a]	EC/YS/C	T	PVB x 4	PR[e]	Brain, lung, RPLN, BHCG, AFP	D	CR (NED necrosis)	6	9
5	S/T	T	PVB X 1	NR[e]	Lung, BHCG, AFP	D	CR	20+	24+
6	S	T	XRT (ID) PVB x 5 Cyclophosphamide PVB XRT (SD)	PR PR PR NR PR	RPLND	B	CR	14	22+
Group B									
7	TER/EC	T	PVB x 4	CR	Lung, mediastinum	D	CR (NED necrosis)	5	7
8	EC	T	PVB x 6 (NED CA)	CR	Lung	B	CR	3	8
9	S	T	XRT (ID) PVB x 4	CR	HCG	E	CR	9+	13+
Group C									
10	TER/EC	T	PVB x 4 BEP x 1 Surgery BEP x 4	PR PR PR	Lung, liver, AFP	D	CR (NED teratoma)	8	12
11	S	T	XRT (ID/SD) PVB x 4 BEP X 4	CR CR CR	Bone, RPLN adrenal, AFP BHCG, thyroid	F	CR	12	17+
12	EC	T	PVB x 4 BEP x 2	PR CR	Lung, RPLN, AFP	C	CR	14+	17+
13	EC	T	XRT (ID) ACT/V/B x 5 V x 7 DOX x 7 CMFO x 2 BCG P x 3 Surgery (lung) DOX Surgery PE	NR NR NR NR NR NR Teratoma NR CR CR	RPLN, AFP	C	CR	6+	7+
14[b]	EC/T	T	PVB PE	CR PR	RPLN, lung AFP	D	CR (NED teratoma	5	24
15[c]	Undifferentiated/T	R	PVBA x 8 PE x 4	PR PR	Lung HCG	E	CR	9	17
16[d]	C/EC/T	T	PVB/PVA x 6 PVB x 4 PE x 4	CR CR CR	RPLN, HCG	C	CR (NED carcinoma)	21+	25+

C, choriocarcinoma; T, teratoma; RP, retroperitoneum; PVB, cisplatin, vinblastine, bleomycin; POB, cisplatin, vincristine, bleomycin; RPLN, retroperitoneal lymph node; XRT, radiation therapy; (ID), infradiaphragmatic; E, embryonal carcinoma; S, seminoma; YS, yolk sac carcinoma

[a] Patient died of pulmonary embolus with no viable tumor at autopsy
[b] Received only two days of IFX 2° to hematuria
[c] Relapsed with brain metastases only treated with XRT
[d] Initial remission to PVB/A lasted 66 months. Subsequent relapse with PVB and PE were 6 months and 14 months, respectively
[e] Markers did not normalize with therapy
[f] See Table 1

known effectiveness of cisplatin plus etoposide as salvage therapy in patients with unresectable PR, but these results compare favorably with our previous experience in such patients.

For patients who have previously received VP 16 plus cisplatin salvage chemotherapy, however, the potential contribution of ifosfamide to the cisplatin/VP 16 combination is easier to document. A patient who has not been cured with the induction therapy or a salvage regimen given in appropriate dosages and at appropriate times and intervals will never, in our experience, achieve a durable CR with the same regimen(s). Thus, in group C, in which all the patients had previously received VP 16 and cisplatin, *any* patient who has a durable CR will demonstrate the therapeutic contribution of ifosfamide.

Indeed, in this latter group, 7/19 (37%) patients achieved CR and 3 (16%) remain free of disease at 9+, 16+, and 25+ months after initiation of chemotherapy. Follow-up is needed, but these results appear quite encouraging as third-line therapy.

Although there were no drug-related deaths in this series, toxicity (particularly myelosuppression) was formidable. Nephrotoxicity was also seen in several patients. As might be expected with drugs that have demonstrated preclinical therapeutic synergy, toxicities from combined agents might also be additive, if not synergistic. The degree of myelosuppression and nephrotoxicity in this series was greater than that usually seen with cisplatin plus VP 16 therapy without ifosfamide.

Another question is whether similar high-dose chemotherapy without ifosfamide with equivalent myelotoxicity could achieve comparable results to VIP chemotherapy. High-dose chemotherapy (usually with VP 16) administered with autologous marrow transplantation is a logical application of this concept. Despite several complete remissions achieved with such approaches in testicular cancer (Table 4), responses are brief and long-term survival has not been observed. High dosages of cisplatin appear to be another practical approach, as a dose-response relationship was observed by the Southwest Oncology Group, which compared 75 mg/m^2 and 120 mg/m^2 in first-line therapy [24]. Ozols et al. extended this concept by using cisplatin 40 mg/m^2 daily for 5 days with hypertonic saline, with encouraging results as first-line therapy in patients with advanced disease [22]. Whether these high dosages of cisplatin can overcome resistance in patients previously treated with conventional cisplatin dosages is uncertain.

Using high doses of cisplatin (40 mg/m^2 daily × 5) with VP 16 (100 g/m^2 daily × 5), Trump and Hortvet recently reported their experience with 12 such patients [30], 3 of whom (25%) had achieved previous short-term CR (3, 3, 5 months) while the remaining 9 had PR as best response to PVB. The median nadir WBC and platelet count were 1200/m^3 and 18500/mm^3, respectively. Therapy was associated with granulocytopenic fever in 14 of 33 cycles. A clinically evident hearing loss developed in 5 patients, although clinically significant renal insufficiency did not occur. Four patients achieved CR (2 chemotherapy only, 2 NED carcinoma). One further patient had radiation therapy to residual abdominal seminoma. Only one patient, however, remained in CR remission 24 months after therapy, the other complete responders relapsing after 2–4 months.

Since the development of effective first-line regimens with cisplatin for testicular cancer, the effect of cyclophosphamide in second-line therapy has been largely unknown. In our experience with a variety of different regimens for cyclophosphamide combination chemotherapy, we have only rarely produced favorable objective responses.

Ifosfamide combination chemotherapy has recently been used by several European investigators to treat testicular cancer. Aigigner et al, used cisplatin plus ifosfamide in 9 patients and achieved CR in 3 of these patients [1]. Scheulen et al. combined ifosfamide + VP 16 for 60 patients, obtaining remissions in 24 (40%) of the patients [28]. Hartenstein et al. used cisplatin + ifosfamide + vinblastine as salvage therapy for patients failing to achieve CR with PVB induction chemotherapy [16], obtaining 7 CRs and 3 PRs in 12 such patients with a mean survival time of 9$^+$ months (range 4–20$^+$ months) for complete responders. Additionally, Bremer et al. used ifosfamide + VP 16 in the treatment of 36 previously treated patients [5]: 3/21 patients with unresectable PR and 1/15 patients with progressive disease attained CR with this combinnation regimen. Although none of these reports gives specific information on response and response duration previous to therapy, they do suggest that ifosfamide combination regimens can indeed be used with acceptable toxicity.

The ultimate role for ifosfamide in the treatment of testicular cancer remains to be determined. Because of its acitivity in highly refractory patients, we feel it is warranted to investigate ifosfamide combination chemotherapy as initial salvage therapy in testicular cancer. We are currently conducting a trial at Indiana University, using such treatment with mesna [8, 17] given by continuous infusion instead of *N*-acetylcysteine.

Table 4. High-dose chemotherapy and autologous marrow transplant in refractory testicular cancer

Authors [ref.]	No. of patients	Chemotherapy regimen	No complete remission %	MDR (weeks)
Blijham et al. [2]	13	CYT/VP-16	4 (30)	15
Corringham et al. [10]	1	Melphalan	0	–
Wolff et al. [36]	11	VP-16	2 (20)	20, 24
Robinson et al. [23]	2	MTX/HN_2/ADM VCR/VLB/MITH/6-TG D-ACT/5FU/CYT/ BCNU/ARA-C/CDDP	0	

CYT, cyclophosphamide; MTX, methotrexate; ADM, adriamycin; VCR, vincristine; VLB, vinbastine; MITH, mithramycin; HN_2, nitrogen mustard; D-ACT, actinomycin D; 5U, 5-fluorouracil; BCNU, bis-chloroethylnitrosourea; ARA-C, cytosine arabinoside; CDDP, cisplatin; 6-TG, 6-thioguanine

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