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Cisplatin, VP-16-213 and MGBG (Methylglyoxal bis guanylhydrazone) combination chemotherapy in refractory lymphoma, a phase II study

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Summary

In an effort to improve the treatment of patients with refractory or recurrent lymphoma, we developed a protocol using cis-platinum combined with two other agents of known efficacy in these disorders but with differing side effects: VP-16 and MGBG. Twenty-six eligible patients were treated with this regimen. There were 15 men and 11 women with a median age of 54 years (22–73), and performance status of 1 (0–3). Their diagnoses were Hodgkin's disease 5 and non-Hodgkin's lymphoma [NHL] 21 which included 11 with diffuse histocytic lymphoma [DHL]. The median number of chemotherapy regimens was 2 (1–5); 12 also received radiotherapy. Twenty patients are evaluable for response: 15 NHL and 5 Hodgkin's disease. Three patients, all of whom had DHL entered complete remission (20%) with a median time to treatment failure of 7½ months. Six NHL (40%) and one Hodgkin's disease (20%) patients entered a partial remission. There were three early deaths: one due to progressive disease, one to acute respiratory failure, and one with disease status undocumented. Toxicity included leukopenia, thrombocytopenia, anorexia, nausea, vomiting, stomatitis, alopecia, renal failure, profound peripheral neuropathy, and hypersensitivity vasculitis. Treatment was stopped because of the latter two. These agents are non-crossresistant with doxorubicin-containing regimens. The drugs are possibly synergistic and modestly active with moderate to severe toxicity.

Introduction

The poor response rate with salvage chemotherapy for patients with lymphoma who have either failed to enter into remission or who have relapsed from their initial combination chemotherapy prompted interest in a new type of drug: cis-diamminedichloroplatinum [1–2]. Following the reports of its efficacy in these patients as a single agent, it was tested in 2 and 3 drug combinations [3–16]. These are summarized in Table 1. We have recently described the results of such a three drug combination. Cisplatin, vinblastine and bleomycin, given to 17 very heavily pretreated patients, yielded responses in 9 (3 complete and 6 partial) [14]. Toxicity included severe myelosuppression and mild decrease in creatinine clearance in patients receiving 2 or more courses. There were no drug related deaths. Most responders achieved partial remission after the first course. Furthermore, many of the nonresponders demonstrated a rapid tumor shrinkage but equally rapid regrowth and thus could not be called responders. These results prompted us to consider another combination with cisplatinum, and we selected VP-16 and MGBG. VP-16 is a synthetic congener of podophyllotoxin, the crystalline extract of the plant podophyllum peltatum. It was shown to have a response rate of 14% in 64 patients with Hodgkin's and 23–32% in over 100 patients with non-Hodgkin's lymphoma [17]. Its major tox-

Table 1. Literature survey

Study	Ref	Drugs	Non-Hodgkin's							Hodgkin's disease						Unknown distribution					
			Total	Eval	CR	%	PR	%	%Total resp	Eval	CR	%	PR	%	%Total resp	Eval	CR	%	PR	%	%Total resp
Rossof	1	PT	25	17			1	6	6	8	1	13	1	13	26						
Cavalli	2	PT	31	19			5	26	26	8	1	13			13						
Bender	21	VP-16	20	19	1	5	7	37	42												
Kroner	5	VP-16	20	13			5	38	38	7			5	71	71						
Knight	22	MGBG	54	44	1	2	8	18	20	10			3	30	30						
Warrell	23	MGBG	46	27			10	37	37	13			6	46	46						
Judson	3	PT VP-16	25	17	5	29	4	24	53												
Kaplan	4	PT VP-16	58	53	6	11	11	21	32												
Kroner	5	PT VP-16	22	18			5	38	38	7			5	71	71						
Von Heyden	6	PT VP-16	15	4			1	25	25	11			2	18	18						
Fosser	7	PT VP-16 PRED	18	6			2	33	33	12	3	25	2	17	41						
Dabich		PT VP-16 MGBG	27	15	3	20	6	40	60	5			1	20	20						
Williams	8	PT VP-16 CCNU BCNU MTX-L	25	18			3	17	17	7	1	14			14						
Silverman	9	PT VP-16 ARA-C	16													15	1	7	9	60	67
Dana	10	PT AMSA MGBG	37	30			13	44	44												
Camacho	11	PT VDS MGBG	16													14	2	14	6	43	57
Tseng	12	PT VM-26 ARA-C	21	21	2	10	7	33	43												
Spiers	13	PT VM-26 BCNU BL DEX	20													13	2	15	5	38	53
Liepman	14	PT VLB BL	17	14	3	21	2	14	35	3			3	100	100						
Corder	15	PT VLB BL	13	13			5	38	38												
Velasquez	16	PT ARA-C DEX	48	43	11	26	11	26	52												

Drugs: BCNU = Carmustine, CCNU = Lomustine, BL-Bleomycin
MTX-L = Methotrexate with leucovorin rescue
VDS = Vindesine, VLB = Velban, VM-26 = Teniposide
PRED = Prednisone, DEX = Dexamethasone
AMSA = Amsacrine, ARA-C = Cytosine arabinoside

Headings: Eval = No. of evaluable patients
CR = No. of complete responders
PR = No. of partial responders

icity is reversible myelosuppression, particularly leukopenia and anemia [17–19]. Methylglyoxal bis guanylhydrazone is a drug in which there is renewed interest. It had been used previously as methy-gag [20–23]. Warrell noted partial responses in 6 of 13 evaluable patients with refractory Hodgkin's disease and 10 of 27 patients with non-Hodgkin's lymphomas [23]. Toxicity was mild and consisted mainly of muscular weakness, myalgia, mucositis, and diarrhea. Myelosuppression was minimal which made this agent attractive for use in combination with myelotoxic drugs.

From January, 1981 until January, 1985 this protocol was used to treat patients with refractory lymphoma, both Hodgkin's and non-Hodgkin's type. We are reporting our results and toxicity in 27 of these patients.

Treatment

The protocol is outlined in Table 2, which also illustrates the adjustment for hematologic nadir and renal impairment. The courses were repeated every 28 days.

Table 2. Protocol

	Drugs	Dose	Days of cycle	
	Cisplatin	60 mg/M^2	1	
	VP-16	80 mg/M^2	1,2,3	
	MGBG	500 mg/M^2	1,8,15	
Modifications: hematologic nadirs				
PMNS	Platelets	CISPT/M^2	VP-16/M/M^2	MGBG[2]
$>1500/mm^3$	$>100{,}000/mm^3$	Same	Increase to 100 mg	Same
$500-999/mm^3$	$50-74{,}999/mm^3$	Same	60mg	Same
<499	$<49{,}999$	60mg	40mg	250mg
Renal				
Rise in maximum serum creatinine above baseline (mg %)				
		CISPT/M^2		MGBG/M^2
	$<.5$	Same		Same
	$>.5$ but $<.75$	Decrease 25%		250mg
	$>.75$ but <1.0	Decrease 50%		250mg
	>1.0	Hold		Hold

Material and methods

Eligibility criteria

All patients with histologically confirmed refractory Hodgkin's or non-Hodgkin's lymphoma who had measurable disease and performance status equal to 3 or better by SWOG group criteria were eligible for entry onto this protocol. Patients with Hodgkin's disease should have received a doxorubicin containing regimen prior to entry onto this study. There were no age restrictions and no limitation on the number of previous regimens. The initial WBC count was to be equal to or greater than 3000/cu mm and the platelet count equal to or greater than 75,000/cu mm. The serum creatinine could be no greater than 1.5 mg%. The creatinine clearance following hydration was to be greater than 50 cc/minute. Patients could have no evidence of active central nervous system involvement. If such disease were present, specific treatment aimed at CNS lymphoma was to be underway before the patient could begin chemotherapy with this program. Patients were to be 3 weeks past previous chemotherapy or radiation therapy at the onset. The period was 4 weeks for patients who had received nitrosoureas. It was necessary for patients to give informed consent in keeping with our institutional policies and a signed statement to that effect was to be a part of the record. We planned to give patients allopurinol unless they were allergic to this medication.

Pretreatment requirements

Pretreatment evaluation included history and physical examination with documentation of symptoms, disease activity, tumor measurements, and performance status. Laboratory parameters included CBC with differential and platelet count, uric acid, electrolytes, magnesium, and liver function studies (SGOT, SGPT, LDH, alkaline phosphatase and bilirubin). To establish the renal function we obtained BUN and serum creatinine, urinalysis with microscopic examination of the sediment and a 24 hour urine for creatinine and protein. IVP or renal

ultrasound was used to rule out hydronephrosis. Other investigations included chest x-ray and electrocardiogram.

Criteria for response

Complete remission (CR) was defined as the disappearance of all clinical evidence of tumor on physical examination, x-ray or biochemical evaluation for more than 1 month. Partial remission (PR) was 50% or greater decrease by physical examination, roentgenogram and/or CT scan in the sum of the products of the perpendicular diameters of all measured lesions lasting more than 1 month. There could be no simultaneous increase in the size of any lesion or appearance of any new lesions. A partial remission in metastatic liver disease consisted of a 50% reduction in the summation of all liver measurements below the costal margin and improvement of abnormal liver function tests to normal. Minor response was a 25% decrease in all measurable disease but less than that required for a partial remission. Stabilization was a less than 25% decrease or increase in measurable disease for more than 2 months. For progression (Progr) there was to be the appearance of either new lesions or a greater than 25% increase in measurable disease. The subjective response was measured by the SWOG performance scale. The duration of response was measured from the initiation of the study until a 25% increase in the sum of all tumor measurements was reached. An adequate trial was defined as one cycle of therapy with objective disease progression or 2 cycles of therapy.

Results

The individual patients are described in Table 3 and toxicity in Table 4. Although 27 patients were entered onto this protocol, one patient with Hodgkin's disease was ineligible because he had not received a doxorubicin containing regimen prior to this therapy. The 26 eligible patients included 15 men and 11 women with a median age of 54 years, range 22 to 73, and a performance status of 1, range 0 to 3. There were 5 with Hodgkin's disease, and 21 with non-Hodgkin's lymphoma, sub-divided into 11 diffuse histiocytic lymphoma (DHL), 3 diffuse mixed lymphoma (DML), 3 diffuse poorly differentiated lymphoma (DPDLL), 2 nodular poorly differentiated lymphocytic lymphoma (NPDLL) and 2 well differentiated lymphocytic lymphoma (WDLL). Bone marrow involvement was present in 6 and bone involvement in 5 patients. These patients were heavily pretreated. The median number of previous chemotherapy regimens was 2 with a range of 1–5. Twelve of the 26 patients had also received radiotherapy at some time. Two patients were treated with less than 1 course, 10 patients 1 course, seven 2, two 3, three 5, two 6 and one 8 courses of cisplatin, VP-16, and MGBG. Patients in PR continued to be treated as long as they responded. Twenty of the twenty six eligible patients, 15 with NHL and 5 with Hodgkin's disease, were evaluable for response. There were three complete remissions in patients with DHL [3/15 NHL = 20%] with time to treatment failure 5, 7½, and 42 months. There were 3 early deaths, one due to disease progression prior to completion of the first course, and one immediately after. Unfortunately the patient was transferred to another hospital and the measurable disease was not documented. The third patient died of acute respiratory failure, the question of its relationship to chemotherapy is not resolved. Two patients had therapy discontinued because of profound peripheral neuropathy and hypersensitivity vasculitis, and one refused to complete the first course.

Treatment in 67 courses resulted in a median white count of 1800/cu mm, range 100–14,200, platelets 93,000/cu mm, range 3200–391,000. The doses were sufficiently high that only 3 patients received the prescribed chemotherapy. Although MGBG should have been given, the usual adjustment for myelosuppression was the withholding of Day 15 and/or Day 8 MGBG. This was done even on the first course. There was severe drug induced renal failure in one patient and modest renal impairment in two others. In one of these there was a response to modulation of dose. Infections occurred in 9 of 67 courses and bleeding in 3. Severe nausea and vomiting was noted at some time in one-

Table 3. Individual patient characteristics

#	Diag	Age	Sex	Race	Previous chemotherapy	Rad	P.S.	B.M.	Bone	Sites of disease	No. of courses	Outcome	Duration months
2	Hodgkins	22	F	W	MOPP, VELB, COP, CHLOP, C-MOPP	No	1			Lung, Nodes	1	PROGR	
3		26	F	W	MOPP, CHOP, PVB	Yes	1		+	Pancreas, Nodes, Flank	2	PR	
5		26	M	W	MOPP, C-MOPP	No	1			Nodes, Kidney	3	INELIG	
11		26	F	W	MOPP, ABVD	Yes	0			Breast mass, Chest wall, Mediastinum	1	PROGR	
18		22	M	W	MOP-BAP	No	1			Adrenal, Mediastinum, Ext Abd dis	1	PROGR	
23		24	F	W	MOPP, ABVD, BCVPP	Yes	0			Nodes	1	PROGR	
7	WDLL	58	M	N	COP, COP, VCR/CHL, AOP, POACH	No	2	+	+	Liver, Nodes	2	PROGR	
12		54	M	W	CHOP, COP, COAP, COMLA	No	0	+		Nodes, Liver, ABD Mass	1	PR	
9	NPDLL	47	F	W	CHOP, X2, PVB, CCNU/PRO, CHL/PRED	No	1			ABD Mass, Nodes	8	PR	
16		37	M	W	CHOP, PVB, CHL/CCNU	No	1	+		Nodes	2	PROGR	
17	DPDLL	51	F	W	CHOP	No	0	+		Nodes	3	PR	
19		68	M	W	CHOP, COP	No	2	+		Nodes, Liver, Lung	1	NE-RFT	
22		61	M	W	CHOP	Yes	1			Abd Mass	<1	NE-TOX[1]	
13	DML	66	M	W	BACOP, CYTOXAN	No	1			Small bowel, Nodes	6	PR	
15		60	M	W	COP, CHLOP, CHOP	Yes	1	+		Lung, Pleura, Chest wall	2	PR	
21		54	F	W	CHOP	No	1			Liver, Nodes, ABD Mass	5	PR	
1	DHL	52	M	B	CHOP, COP, ARA-C-MTX	Yes	0			Lung, Nodes	6	CR	7 1/2
4		41	M	W	BACOP, ARA-C-MTX	Brain	1			Abd wall, CSF	2	PROGR	
6		63	F	W	CHOP, COP-BL	Yes	1			Abd	2	PROGR	
8		31	M	W	CHOP, HIGH DOSE ADRIA	No	1		+	Tonsils, Nodes, Liver	2	PROGR	
10		70	F	W	CHOP	No	1			Nodes	1	NE-ED	
14		54	M	W	CHOP	Yes	1			Nodes, Skin, CNS, Abd mass	5	CR	5
20		49	F	W	HIGH DOSE ADRIA	Yes	0		+	Nodes, Palate	5	CR	42
24		43	F	W	CHOP	Yes	0		+	Nodes	1	PROGR	
25		61	M	W	CHOP, MOPP	Yes	0			Liver, Nodes	1	NE-TOX[2]	
26		73	M	B	CHOP	No	3			Tonsils, Nodes	<1	NE-ED	
27		51	M	W	BACOP	Yes	1			Abd mass, Nodes	1	NE-ED	

Summary: CR-3, PR-7, PROGR-10, NE-ED-3, TOX-2, INELIG-1, RFT-1

[1]Severe neuropathy
[2]Hypersensitivity vasculitis

Drug combinations

ABVD: Adriamycin, Bleomycin, Vinblastine, DTIC

AOP: Adriamycn, Vincristine, Prednisone

ARA-C-MTX: Cytosine Arabinoside-Methotrexate

BACOP: Bleomycin, Adriamycin, Cyclophosphamide, Vincristine, Prednisone

BCVPP: BCNU, Cyclophosphamide, Vinblastine, Procarbazine, Prednisone

CCNU/PRO: CCNU/Procarbazine

CHL-O-P: Chlorambucil, Vincristine, Prednisone

CHL/PRED: Chlorambucil/Prednisone

CHOP: Cyclophosphamide, Adriamycin, Vincristine, Prednisone

C-MOPP: Cyclosphosphamide, Vincristine, Procarbazine, Prednisone

COAP: Cyclophosphamide, Vincristine, Cytosine Arabinoside, Prednisone

COMLA: Cyclophosphamide, Vincristine, Methotrexate, Levcovorin, Adriamycin

COP: Cyclophosphamide, Vincristine, Prednisone

COP-BL: Cyclophosphamide, Vincristine, Prednisone, Bleomycin

HIGH DOSE ADRIA: Adriamycin, Vincristine, Prednisone, Cytosine Arabinoside, Cyclophosphamide

MOP-BAP: Nitrogen Mustard, Vincristine, Procarbazine, Bleomycin, Adriamycin, Prednisone

MOPP: Nitrogen Mustard, Vincristine, Procarbazine, Prednisone

POACH: Prednisone, Vincristine, Cytosine Arabinoside, Cyclophosphamide, Adriamycin

PVB: Platinum, Vinblastine, Bleomycin

VELB Vinblastine

VCR/CHL: Vincristine/Chlorambucil

Table 4. Toxicity

WBC median 1800/cu mm (100–14,200)		
Platelets 93,000/cu mm (3200–391,000)		
≥3 N/V or	>5 emesis/day	9/27 patients
≥3 Anorexia or	5–10% wt loss	1/27 patients
≥3 Stomatitis or	>3 discrete ulcers	2/27 patients
Hepatic		0/27 patients
≥2 Renal or	Bun 51–75 or creatinine 2.6–3.0 mg/dl.	3/27 patients*
≥3 CNS or	severe paresthesias	1/27 patients
≥3 Skin or	moist disquamation with ulceration	1/27 patients
≥2 Alopecia or	pronounced hair loss	1/27 patients
Infections	9/67 courses	
Bleeding	3/67 courses	

* Responded to change in dose: 1/3 patients

third of the patients, but severe diarrhea occurred in only 1 patient and stomatitis in 2. As noted there was discontinuation of protocol due to severe peripheral neuropathy in one patient and to skin hypersensitivity in another. Alopecia was not a problem. Hypoglycemia was not seen.

Discussion

The addition of other agents to cis-platinum seems to confer some added efficacy, since results with cis-platinum as a single agent were modest with few complete responders (Table 1). Unfortunately, the small numbers of patients and the relatively large numbers of protocols with different doses and schedules preclude the use of statistical analysis to sort out the contribution of each agent. For example, Judson and Wiltshaw, [3] i.e., used a dose schedule of cis-platinum 50 mg/m^2 i.v. daily with hydration plus VP-16 100 mg/m^2 i.v. days 1–3, repeated every 3 weeks, whereas Kaplan *et al.* [4] administered cis-platinum 20 mg/m^2 and VP-16 80 mg/m^2, both daily for 5 days every 3–4 weeks. The Judson and Wiltshaw regimen produced the best complete response rate (29%) in patients with non-Hodgkin's lymphoma, but it was only of 12 weeks duration. The combination of cis-platinum, cytosine arabinoside and decadron also resulted in a significant complete response (26%) with a more durable remission. Like these latter investigators we achieved our best responses in patients with large cell lymphoma, all of whom had been treated initially with doxorubicin containing regimens, suggesting these drugs are non-cross resistant with the front line therapy. One of the responders had received multiple combinations [3] prior to this one. The remissions were fairly long-lived with a median time to treatment failure of 7½ (5–42) months, but the CR rate (20%) is not as good than that of the cytosine arabinoside combination. Toxicity was moderately severe and, mainly, reversible. Renal impairment persisted in 2/3 patients.

In summary, the combination of cis-platinum, VP-16 and MGBG constitutes a modestly active and moderately to severely toxic regimen for the management of patients with relapsed lymphoma. Its efficacy in this group of patients might warrant further exploration of these potentially synergistic drugs in protocols with refractory aggressive lymphomas.

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