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Cis-dichlorodiammineplatinum (Cis-platinum) and etoposide (VP-16) in malignant lymphoma – an effective salvage regimen

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Summary. *Response rates in malignant lymphoma after failure of first-line therapy are generally poor. Twenty-five patients with non-Hodgkin's lymphoma (NHL) unresponsive to standard combination chemotherapy were treated with cis-platinum/VP-16. All were heavily pretreated, 29% having received three or more different drug regimens. Seventeen patients were evaluable for response. There were five complete remissions (CR) (29%) and four partial remissions (PR) (24%), giving an overall response rate of 53% (36% of all patients treated). The duration of CR was 12–48 weeks. Median survival for responders was 25 weeks (15–95), compared with only 5 weeks (4–17) for non-responders (P = 0.002). Toxicity included nausea and vomiting, alopecia, minor renal impairment, and myelosuppression. This was sometimes severe: WBC <1.0 × 10^9/l in three patients (18%) and platelets <50 × 10^9/l in five patients (29%). The response rate for this combination is superior to that reported for either cisplatinum or VP-16 alone in similar patients (PR only 26% and 20%–30%, respectively). Further investigation is required to define the role of these drugs in the first-line treatment of poor-prognosis NHL.*

Introduction

Satisfactory remission rats can now be obtained in diffuse aggressive-histology NHL with a variety of chemotherapeutic regimens [6, 9, 12]. A proportion of patients will experience a long CR and may be cured. However, as many as 50% of patients who achieved CR will relapse, and subsequent responses are usually incomplete and of limited duration. Similar difficulty is experienced in the treatment of nodular lymphomas that have entered an aggressive phase with the appearance of locally invasive lesions. Phase-II trials of *cis*-platinum and VP-16 in such patients yielded only partial responses: with *cis*-platinum in 26% [5], and with VP-16 in 20%–30% [7, 10, 14]. We have investigated the use of these two agents in combination.

Methods

The dose schedule used was a single injection of *cis*-platinum 50 mg/m^2 IV with hydration, plus VP-16 100 mg/m^2 IV daily for 3 days, repeated 3-weekly. All patients had relapsed or failed to respond to standard combination chemotherapy. They were heavily pretreated; 65% had received prior radiotherapy plus chemotherapy, while 29% had been given three or more different drug combinations.

Ten patients had diffuse histiocytic (DH) or poorly differentiated lymphocytic lymphoma (PDLD); four had nodular lymphoma in the final progressive stage of the disease; one had T-cell lymphoma (which has been regarded as PDLD); one, malignant histiocytosis; and one remained unclassified due to the extremely pleomorphic nature of the disease.

The patients' full blood count (FBC), platelets, urea, and creatinine were recorded prior to each treatment, and where possible the white blood cell (WBC) and platelet nadirs were measured at 2 weeks. A significant (> 25%) rise in creatinine was investigated by ^{51}Cr-labelled EDTA clearance and the dose of *cis*-platinum was reduced by 50% if the glomerular filtration rate (GFR) fell below 50 ml/min; the dose of VP-16 was usually reduced by 30% if the WBC nadir was < 1.0 × 10^9/l or platelets < 50 × 10^9/l.

Complete remission was defined as complete regression of all identifiable disease maintained for at least 3 months and confirmed by re-staging investigations such as bone marrow examination, liver biopsy, or abdominal CT scan where appropriate. Partial remission required a greater than 50% reduction in the size of all the measurable lesions, without the appearance of any new lesions and maintained for at least 1 month.

Life-table analysis was performed by the method of Kaplan and Meier.

Results

Twenty-five patients received *cis*-platinum/VP-16 between April 1979 and June 1983. The mean number of courses given was 3. Two patients were not evaluable because of (a) loss to follow-up and (b) progression and death due to central nervous system (CNS) disease, other disease being occult. Six other patients died within a short time after the first course of treatment and therefore could not be assessed for response, although they must be regarded as treatment failures. Their survival ranged from 3 to 21 days, with a median of 16 days. These patients were excluded from the detailed analysis.

The pretreatment characteristics of the 17 fully evaluable patients are given in Table 1, which shows that 11 had received prior radiotherapy and five had been given three or more

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Table 1. Pretreatment characteristics of evaluable patients

Pretreatment characteristics	No. of patients (%)
Median age 45 (11–68)	
Male	11
Female	6
Previous radiotherapy	11 (65)
Previous CR	8 (47)
Progressive disease during chemotherapy	14 (82)
Previous chemotherapy regimes:	
1 combination	8 (47)
2 combinations	4 (23)
3 or more	5 (29)

Histology		Response	
		CR	PR
PDLD	4	1	–
DHL	6	1	3
MHLD	1	1	–
PDLN	2	1	1
MHLN	2	–	–
Unclassified lymphoma (UL)	1	–	–
Malignant histiocytosis (MH)	1	1	–

Table 2. Response to Cis-platinum/VP 16

	No.	%	Median duration response in weeks (range)	Median survival in weeks (range)
Complete response	5	29	12 (12–48)	25 (15–95)
Partial response	4	24	11 (8–28)	31 (15–49)
No response	8	47	–	5 (4–17)

Overall response rate = 53% (36% of all patients treated)

different drug combinations, including COP, CHOP-Bleo, and M-BACOP.

There were five complete remissions and four partial remissions, giving an overall response rate of 53% (36% of all patients treated). The median duration of CR was 12 weeks (12–48) and that of PR, 11 weeks (8–28). Response falling short of PR was seen in a further four patients. These results are summarized in Table 2. Median survival for all responders was 25 weeks, compared with only 5 weeks for non-responders ($P = 0.002$, log rank test). The actuarial survival according to CR and PR is shown in Fig. 1. There was a suggestion that the response rate was better in less heavily pretreated patients, in that the median duration of previous therapy was 12 months for non-responders but 6 months for responders. There was no correlation between response and number of different treatments.

The response details in relation to histology and previous treatment are summarized in Table 3. Patient 1 relapsed after 14 months and achieved a second CR with *cis*-platinum/VP-16. Four patients died of CNS problems; patient 3 developed a confusional state then coma, which the EEG suggested was due to progressive multifocal leukoencephalopathy (PML). This was confirmed by post-mortem brain biopsy, and there was no evidence of active lymphoma at the time of death. Patient 4 relapsed in the CNS but had no signs of systemic disease at death. Patients 8 and 15 died of CNS disease as part of generalized disease progression.

Toxicity was moderately severe. All patients experienced significant nausea and vomiting plus alopecia. Renal impairment was usually only minor, the mean increment in plasma creatinine at the end of treatment being 21 mmol/l (0–66). Only two patients received a reduced dose of *cis*-platinum because of a low GFR. Myelosuppression was more marked. The WBC and platelet nadirs were seen at 12–14 days and the mean values were WBC 2.3×10^9/l and platelets 123×10^9/l. A WBC $<1.0 \times 10^9$/l was seen during five courses in three patients (18%) and platelets $<50 \times 10^9$/l during seven courses in five patients (29%). There was one possibly treatment-re-

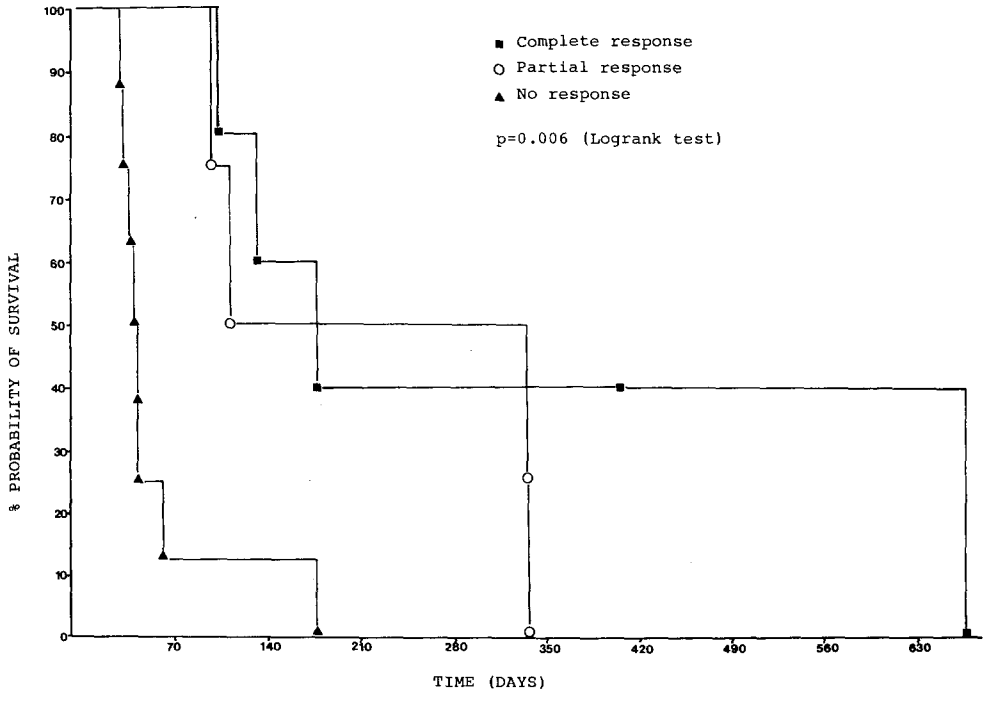

Fig. 1. Actuarial probability of survival according to CR and PR

Table 3. Response referred to histology and previous treatment

Number	Age	Histology	Previous treatment (response: duration in weeks)[a]		Sites of major disease; Prior to *cis*-plat/VP-16	Response[a] (duration in weeks)	Survival (weeks)	Comment
1	68	MH	DXT COP Adr/Cyt	(NR) (NR) (NR)	Nodes, bone	CR (48)	95	2nd CR with *cis*-plat/VP-16
2	61	PDLD	COP + DXT	(PR:20)	Liver, pleura lung	CR (20)	58+	Minor relapse in different site
3	27	DHL	DXT CHOP + cranial DXT	(CR:8) (CR:10)	Liver, soft tissue, CNS	CR (12)	19	Death due to PML
4	61	PDLN	COP + Chl/Pred Chl/Pred + DXT Bleo/VCR	(CR:150) (CR:6) (NR)	Hilar nodes, pleura soft tissue	CR (12)	15	Death due to CNS relapse only
5	15	MHLD	VAC COP CHOP + Cyt/Asp	(NR) (NR) (NR)	Abdomen	CR (12)	25	Death due to lymphoma
6	56	PDLN	COP/Chl/Pred Upper & lower Hemibody DXT	(PR:20) CR:50	Nodes, liver, spleen pleura	PR (14)	49	Death due to generalised disease progression
7	22	DHL	COP	(PR:8)	Nodes, skin, pleura	PR (24)	48	Death due to lymphoma
8	21	DHL	BACOP	(PR:7)	Nodes, skin, abdo mass CNS	PR (8)	15	Death due to CNS disease
9	28	DHL	COP/Melph/Pred/ DXT CHOP/Cyt/Asp	(PR:32) (NR)	Nodes, abdo, soft tissue	PR (8)	15	Death due to septicaemia, off treatment following relapse
10	55	PDLD (Thyroid)	DXT	(CR:200)	Nodes, skin, abdo	NR	17	Minimal short-lived response
11	64	PDLD	COP CHOP/Cyt/Asp/DXT	(CR:12) (PR:8)	Nodes, lung	NR	4	
12	50	UL	Chl/Pred COP CHOP/Cyt/Asp	(NR) (NR) (NR)	Nodes, liver, skin, bone marrow	NR	4	Lymphadenopathy improved, died of marrow failure and sepsis
13	43	MHLN	Chl/Pred COP/Splenectomy DXT	(PR:72) (PR:32) (NR)	Nodes soft tissue	NR	5	Soft tissue lesion regressed
14	31	MHLN	Chl Chl Chl DXT	(CR:104) (CR:104) (NR) (NR)	Nodes, bone marrow	NR	6	
15	17	PDLD	COP/DXT + 6MP/M TX	(CR:104)	Bone marrow, CNS, pleura	NR	4	Died due to CNS disease
16	45	DHL	COP/DXT COP/Bleo	(CR:25) (NR)	Nodes, abdo	NR	6	
17	11	DHL	COP	(NR)	Abdo	NR	8	

[a] DXT, radiotherapy; P, prednisolone; Chl, chlorambucil; VAC, vincristine, actinomycin D, cyclophosphamide; BACOP, bleomycin, adriamycin and COP; C, cyclophosphamide; VCR/O, vincristine; H/Adr, adriamycin; Cyt, Cytosine arabinoside; Bleo, bleomycin; CR, complete response; PR, partial response; NR, no response; PML, progressive multifocal leukoencephalopathy

lated death due to sepsis, in a patient (no. 12) with pre-existing marrow failure due to infiltration by lymphoma. Only three patients received a reduced dose of VP-16 because of myelosuppression. No patient developed significant peripheral neuropathy or hearing loss.

Discussion

Combination chemotherapy with regimens such as CHOP and M-BACOD has improved the treatment of advanced-stage diffuse NHL, in that 60%–85% of patients with stages III and IV DH lymphoma can be expected to achieve CR [9, 12]. However, as many as 50% of these are likely to relapse within 2 years, and their survival is then extremely short, i.e., about 3 months in the absence of effective treatment [2, 3]. The outlook is even worse if stage IV patients alone are considered, or those with PDLD, who appear much more likely to relapse late.

The subsequent treatment of patients with advanced NHL who relapse or prove resistant to standard combination

chemotherapy is extremely disappointing. Few single chemotherapeutic agents produce a response rate of more that 25% with very few complete remissions [5, 7, 10, 14]. A combination consisting of ifosfamide, methotrexate, and VP-16 produced a response rate of 62% [3] in a group of relapsed patients with NHL, which is an impressive result for a salvage regimen. In this study *cis*-platinum 50 mg/m^2 in combination with the same dose of VP-16 (100 mg/m^2 × 3) gave a response rate of 53% in a group of heavily pretreated patients who were not responsive to standard chemotherapy. The treatment received prior to cisplatinum/VP-16 is shown in Table 3. Only eight patients had previously been in CR prior to relapse, and 14 had progressive disease (PD) during chemotherapy. The prognosis for such patients is extremely poor. These results may not be directly comparable with those described in other reports of second-line chemotherapy, which also refer to patients who have failed to achieve a rapid CR with standard treatment [3]. Cabanillas et al. make the point that early introduction of second-line treatment carries the best chance of success, as shown by the fact that their best results were obtained with patients in PR. A prospective randomized trial in a large number of patients would be required to allow statistical comparisons between different salvage treatments.

Effective alternative drug combinations are needed, not only for those patients who have failed on first-line treatment but also for inclusion in regimens using a number of different non-cross-resistant combinations in a sequential or alternating fashion. This approach has been successfully applied in NHL [4] and in Hodgkin's disease [1, 13] and there is also theoretical support for its use as a means of overcoming the development of drug resistance [8]. These preliminary results with *cis*-platinum/VP-16 suggest that regimens including this combination deserve further evaluation, possibly as first-line therapy for poor-prognosis NHL.

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